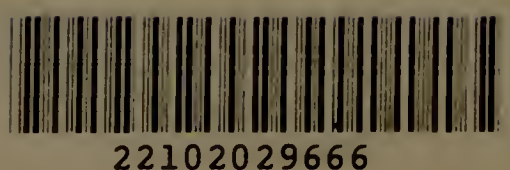
PHARMACOLOGY

OF

ETHYL CHLORIDE.

FIELDEN.



Dr Howard Stevenson
With Kind regards
J. G. L. F.

A CONTRIBUTION

.. TO THE ..

PHARMACOLOGY

.. OF ..

ETHYL CHLORIDE,

.. BY ..

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PREFACE.

THIS "Contribution to the Pharmacology of Ethyl Chloride" was presented this summer to the Queen's University of Belfast as a thesis, and gained the degree of M.D. with a Gold Medal. It is an attempt to add to the limited knowledge of the action of an anaesthetic which is now largely used, but whose pharmacological effects have not received much attention.

I much regret that on account of the magnitude and number of the records of my experiments it is impossible to reproduce them. Forty-eight have been bound and deposited in the library of the Queen's University, where they can be studied by anyone desirous of doing so. On page 4 will be found a tabulated list of experiments, and on pages 12 to 27 notes of most of those used in the preparation of this monograph are detailed.

I desire to express my indebtedness for a grant from the University towards the expenses incurred during this research.

V. G. L. F.

84, DUBLIN ROAD,
BELFAST, July, 1912.

CONTENTS.

RECORDS.

Forty-eight original records, bound separately, include the following seventeen experiments:

Experiment A. Effect of ethyl chloride, ethyl chloride + oxygen and ethyl chloride + CO_2 upon the heart, respiration, and blood pressure—vagi intact and vagi cut.

Experiment B. Effect of ethyl chloride upon respiration and blood pressure—vagi cut.

Experiment C. Effect of ethyl chloride upon kidney volume and blood pressure—vagi intact and vagi cut.

Experiment D. Effect of ethyl chloride, CO_2, and ethyl chloride + CO_2 upon respiration and blood pressure—vagi intact.

Experiment E. Effect of ethyl chloride + oxygen, ethyl chloride + CO_2 and ethyl chloride upon respiration and blood pressure—vagi intact.

Experiment F. Effect upon the heart of ethyl chloride with vagi intact—and of ethyl chloride, ethyl chloride + oxygen and ethyl chloride + CO_2 with vagi cut.

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Experiment L. Effect upon the heart of ethyl chloride—vagi intact and vagi cut.

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Experiment N. Effect of ethyl chloride and ethyl chloride + CO_2 upon respiration and blood pressure—vagi intact.

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Experiment P. Effect of ethyl chloride upon the frog's heart, by perfusion.

Experiment Q. Effect of ethyl chloride upon the frog's heart, by perfusion.

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DIAGRAMS.

A Contribution to the Pharmacology of Ethyl Chloride.

Introduction.

Although ethyl chloride was found to act as a general anaesthetic by Flourens in 1847, and was used for the performance of a surgical operation in the following year by Heyfelder, it fell into disuse. Sir Benjamin Ward Richardson investigated the action of this drug and expressed himself thus [1] :—"The density of the vapour, taking hydrogen as unity, is 32·25. The period for producing narcotism with this vapour is, of necessity, prolonged, and the vapour requires to be pushed freely and vigorously into the chamber or it will produce little more than excitement. The excitement is rather great, but in a minute or two the animal succumbs. The breathing is short and oppressed and the anaesthesia is not deep. During recovery there will possibly be some convulsive action." He refers to it as a good anaesthetic, but his difficulty was to store it. He found its boiling point to be 52°F., and he had "therefore to keep it by saturating common ether with it."

A committee of the British Medical Association appointed in 1877 investigated various anaesthetics and stated, in an interim report in January, 1879, and repeated it in its final report in September, 1880, that ethyl chloride "produced rapid anaesthesia, but in one case the respirations soon stopped, and in another, when air was admitted more freely, general convulsions occurred." The committee's verdict was—"It is apparent that the above substances (including ethyl chloride) all present disadvantages which render them unsuitable for general use as anaesthetics."

The drug remained unemployed till 1895, when Carlson of Gothenburg found that general anaesthesia resulted in two patients upon whom he employed it with the intention of producing local anaesthesia of the gums for dental extraction. From this date the drug was seriously studied as a general anaesthetic, Hacker and Ludwig [2] being perhaps the earliest workers in this domain.

It was not till February, 1901, that I first saw it administered as "Kelene" for a short dental operation. The note, which I took at the same time, mentions that the administration was for 80″, anaesthesia lasted 2′, during which 8 or 10 teeth were removed. Twenty-two c.c. were used, some of which soaked the cotton wool in the inhaler and some fell through on to the patient's face. The inhaler sold and used at that time for the administration was faulty and was soon

discarded by anaesthetists. About two years later I visited the theatres of some of the London hospitals, and at one I saw ethyl chloride (instead of nitrous oxide) used as a preliminary to ether administration. I began to use the drug in August, 1903, and have continued to employ it regularly for the performance of operations over periods varying from a few seconds to 25 minutes. There is scarcely a possibility of its being again discarded, and that we might know more of its action I undertook some systematic work on its pharmacology, and I desire to thank most cordially Professor T. H. Milroy, in whose laboratory I worked, for valuable assistance in starting me properly in the investigation and for much excellent advice and help during its progress, as well as for the use of the apparatus necessary.

On looking up the literature of ethyl chloride I found that many papers and notes had been written, but they nearly all dealt with the clinical use of the drug. There are five papers on its pharmacology which I have been able to avail myself of—one by E. H. Embley, Melbourne [3]; one by W. Webster, Manitoba [4]; one by S. W. Cole, Cambridge [5]; and two by Camus and Nicloux, Paris [6]. Webster and Cole each investigated somnoform, which is a mixture of ethyl chloride 60, methyl chloride 35, and ethyl bromide 5 parts. M'Cardie, in an excellent paper [7], not only gives his own clinical results but refers to both clinical and experimental results of others.

Ethyl chloride, C_2H_5Cl, is a colourless very volatile liquid, its boiling point being 12·5°C. Its vapour density is 2·219 (air = 1), and its specific gravity is quoted by the manufacturers as ·920. It is sparingly soluble in water, but dissolves readily in alcohol, and it should not have an acid reaction.

Embley [3] investigated its solubility and found that it is soluble in water to the extent of 253·36% by volume (0·678% by weight) at 21°C. and 760 m.m. He experienced great difficulty in estimating its solubility in blood in consequence of the blood, as the absorption increased, becoming of a tarry consistence. The difficulty was so enormous that the *complete* absorptive power of the blood for ethyl chloride was not determined. He discovered, however, "that blood at 38°C. takes up an amount exceeding 500% by volume of the vapour," and he states, as a result of his investigation, that "blood absorbs more than twice as much of the gas as water under similar conditions. Ethyl chloride, like chloroform, evidently enters into chemical union with the blood." Camus and Nicloux [6] have very thoroughly gone into the question of the amount of ethyl chloride absorbed by the blood during anaesthesia. They have demonstrated that just as anaesthesia occurs (as the corneal reflex is abolished) the blood contains about 25 m.grm. ethyl chloride per 100 c.c. blood, and that the amount that can be taken up by it varies within very wide limits—from 25 to 200 m.grm. per 100 c.c.—and the more slowly it is inhaled the larger is the amount that can be retained by it without causing death of the animal. They have also shown that the corpuscles absorb about three times as much as the plasma,

and as Embley considers that ethyl chloride evidently enters into chemical union with the blood, I think we are justified in assuming that the opinion held by the special chloroform committee (B.M.A.)[8] regarding chloroform probably maintains for ethyl chloride, viz. : that blood "does not act as a simple solvent, but rather as a temporary retaining and restraining medium that helps to convert irregular into constant flow."

Professor Milroy found that 6 c.c. ethyl chloride in 18,000 c.c. (18 litres) air make a mixture having a strength of 10 % ethyl chloride vapour. Hewitt[9] mentions 5 c.c. to 16,250 c.c. air as equal to 9·3 % vapour, which is identical with Professor Milroy's independent estimate.

Elimination of ethyl chloride is due to pulmonary ventilation, and is very rapid if respiration is normal. It is slowed or suspended if the animal is asphyxiated. During anaesthesia arterial blood contains more ethyl chloride, whilst during recovery it contains less than venous blood (Camus and Nicloux).

SCOPE OF THIS INVESTIGATION.

In my experiments dogs, cats, rabbits, and frogs were employed, and the ethyl chloride used throughout was that manufactured by one firm, but obtained locally from a retail dealer. Ether was always given as the anaesthetic for the preliminary preparations, in two experiments was morphia also given.

The following is the scope of the investigation : -

(I.) The effect, by inhalation, of ethyl chloride with air, or with oxygen, or with oxygen and air, or with CO_2 and air

- (a) On Blood Pressure ;
- (b) On Respiration ;
- (c) On the Heart ;

With intact and with cut vagi.

(II.) The effect on the Isolated Heart—by perfusion

- (a) Of the frog ;
- (b) Of the mammal.

(III.) The effect on the Blood Vessels

- (a) By perfusion of the frog ;
- (b) By volume records of the kidney.

METHODS AND APPARATUS.

I shall first describe the methods employed and the apparatus used in conducting the various sections of the enquiry. A revolving drum with blackened paper was common to all the experiments except in the case of perfusion of the blood vessels of the frog.

(I.) The INHALATION experiments were conducted as follows:—The animal having been anaesthetised with ether the trachea was opened and a Y-tube securely tied in. To one limb was attached an inspiratory, and to the other an expiratory valve. In the earlier experiments the anaesthetic mixtures were made in a rubber bag, capable of holding 3 litres, but the small size was soon found to be very unsatisfactory and was replaced by one having a capacity of 18 litres. This was used throughout the enquiry when once instituted. Administration of the anaesthetic mixture was conducted by attaching the bag to the inspiratory limb of the tracheal tube, or to the inspiratory tube of the respiration pump when the latter was employed.

Blood Pressure. This was recorded by inserting a canula into either carotid artery and attaching it by means of rubber tubing, filled with a solution of magnesium sulphate, to a mercury manometer with a float which carried the recording point.

Respirations were recorded in either of two ways.

(1.) In the case of a large animal a double tambour was bound to the chest wall, and was connected by rubber tubing to a tambour which bore the recording lever.

(2.) In smaller animals instead of a tambour applied to the chest wall a T-tube was inserted between the limb of the Y-tube and the expiratory valve, the tail of the T-tube being connected by tubing with the tambour carrying the recording lever.

Heart records were obtained either—

(1.) By inserting a needle through the chest wall into the cardiac muscle, and attaching the free end of the needle to a tambour which in turn was connected by rubber tubing to another tambour bearing the recording lever. By this method the bag containing the anaesthetic vapour was attached directly to the inspiratory valve.

(2.) By opening the thorax and conducting artificial respiration with a respiration pump, the heart was gently raised from the pericardial sac and passed through a rubber diaphragm into a thistle-tube, the stem of which was attached by a rubber tube to a tambour bearing the recording lever. Two experiments were performed in this way, but one was very unsatisfactory from the fact that the diaphragm through which the heart was introduced responded to the cardiac

impulse to such an extent that the tambour was scarcely affected. The bag of vapour was, in this method, attached to the inspiration tube of the respiration pump.

(3.) By opening the thorax and conducting artificial respiration (as in the previous method) and using two double tambours (designed by Professor Milroy). Each tambour is like a small drum bearing a rubber diaphragm on each side, and to each diaphragm is attached an arm. The heart was placed between the four arms of the two tambours, those of one tambour being attached by threads to the auricles, and those of the second to the ventricles. These tambours were connected by tubes to two tambours carrying recording levers, so that a tracing of the auricular, and another of the ventricular, beat were obtained. Here also the bag of anaesthetic vapour was attached to the inspiratory tube of the respiration pump and forced into the lungs.

I may here mention that the form of respiration pump used had a double action. It forced air (or, when the bag was attached, the anaesthetic vapour) into the lungs and extracted the expired air by alternate actions.

A base-line pointer and another to record the time in seconds, in addition to the revolving drum and blackened paper, completed the apparatus.

(II.) Perfusion of the isolated heart

(a) Of the frog ;
(b) Of the mammal.

(a) Fuhner's apparatus was employed in the case of frogs. It consists of a glass barrel about two inches long and an inch and a half in diameter, into each end of which is fitted a perforated cork. Through the upper passes a glass canula drawn out to a fine but blunt point. This pointed end is passed into the aorta and through the aortic valves of the heart of a frog, which had been excised after pithing the animal, a thread being used to securely fasten the aorta around the canula. Down this canula is passed a finer one, into which flows the perfusing fluid from a Wolff's bottle, so arranged that the pressure is constant. The fluid is drawn off from the ventricle through the outer canula by syphonage, as well as by the pressure of the incoming fluid. Another thread, tied to the extreme apex of the heart, is passed through the perforation in the lower cork and then fastened to lever which records its movements on a revolving drum carrying blackened paper. A modification was sometimes adopted by removing the inner canula and Wolff's bottle and pipetting the various fluids into the tube tied into the heart. When this was done the fluid was frequently changed in the tube by means of the pipette. A second tube through the upper cork can be used to moisten the surface of the heart or some cotton wool contained in the barrel to keep the air and heart moist.

(b) Perfusion of the mammalian heart was carried out by means of Brodie's apparatus. In this, a glass canula is passed into the aorta of the excised heart

(but not through the semilunar valves as the fluid is to perfuse through the coronary vessels) and securely fastened by means of a thread. The canula fits upon the end of a glass tube, which is contained within, and can be drawn up into, a glass chamber which, in turn, is surrounded by a glass water jacket in which warm water is kept circulating to maintain the temperature of the heart and perfusion fluid The latter, after being warmed, passes through the innermost tube and canula into the aorta, thence into the coronary arteries, veins, and right side of the heart from which it exudes through the cut ends of the venæ cavæ to fall into a receptacle. Thermometers in the innermost tube as well as the water-bath used to heat the fluid prior to perfusion assist in regulating the temperature of the fluid, and a thermometer in the water jacket, as well as another in the receptacle containing water in which a worm is placed conveying warm water to the jacket, enable us to regulate the temperature of the water in the jacket and consequently of the perfusion fluid and heart. To obtain the necessary record, a thread, which had previously been attached to the extreme apex of the heart, is fastened to a lever which records the heart beats on the blackened paper upon the revolving drum.

(III.) Effects on the Vessels

(a) By perfusion of the vessels of the frog ;

(b) By volume records of the kidney.

(a) The perfusion of the blood vessels of the frog was carried out as follows:— After killing the animal the thorax and abdomen were opened and a glass canula was fastened into the aorta towards its periphery. The sinus venosus was opened, and the frog suspended head upwards, when fluid, under constant pressure from a Wolff's bottle, was allowed to flow through the canula whence it passed into the arteries and veins and gained exit through the opening made in the sinus venosus. As the fluids gravitated towards, and dropped from, the most dependent part (the feet) of the animal the drops per minute were counted.

(b) The kidney volume was estimated by preparing the animal, as already mentioned in the inhalation experiments, as far as concerned the opening of the trachea and attaching the valves and also for the introduction of a canula into the carotid artery to record blood pressure. In addition, the kidney was withdrawn through a lumbar incision and placed in an oncometer which, by means of vaseline and cotton wool, was closed as securely as possible over the kidney and its pedicle. From the oncometer a tube was led and connected with a tambour bearing a recording lever. A.B.P. tracing and a tracing of kidney volume were obtained by the revolving drum.

NOTES OF THE EXPERIMENTS.

I now give notes of the principal experiments upon which this thesis is based, the analyses of the notes as they concern the various functions follow in the subsequent chapters.

Experiment A. A dog was given morphia and ether for the preliminary preparation of the animal. This experiment was performed to demonstrate the effect of ethyl chloride upon the Heart, Respiration, and Blood Pressure, with vagi intact and vagi cut.

Heart by a needle in the apex through the thoracic wall.

Respiration by the T-tube method.

Blood Pressure by a canula in the carotid.

Vagi Intact.

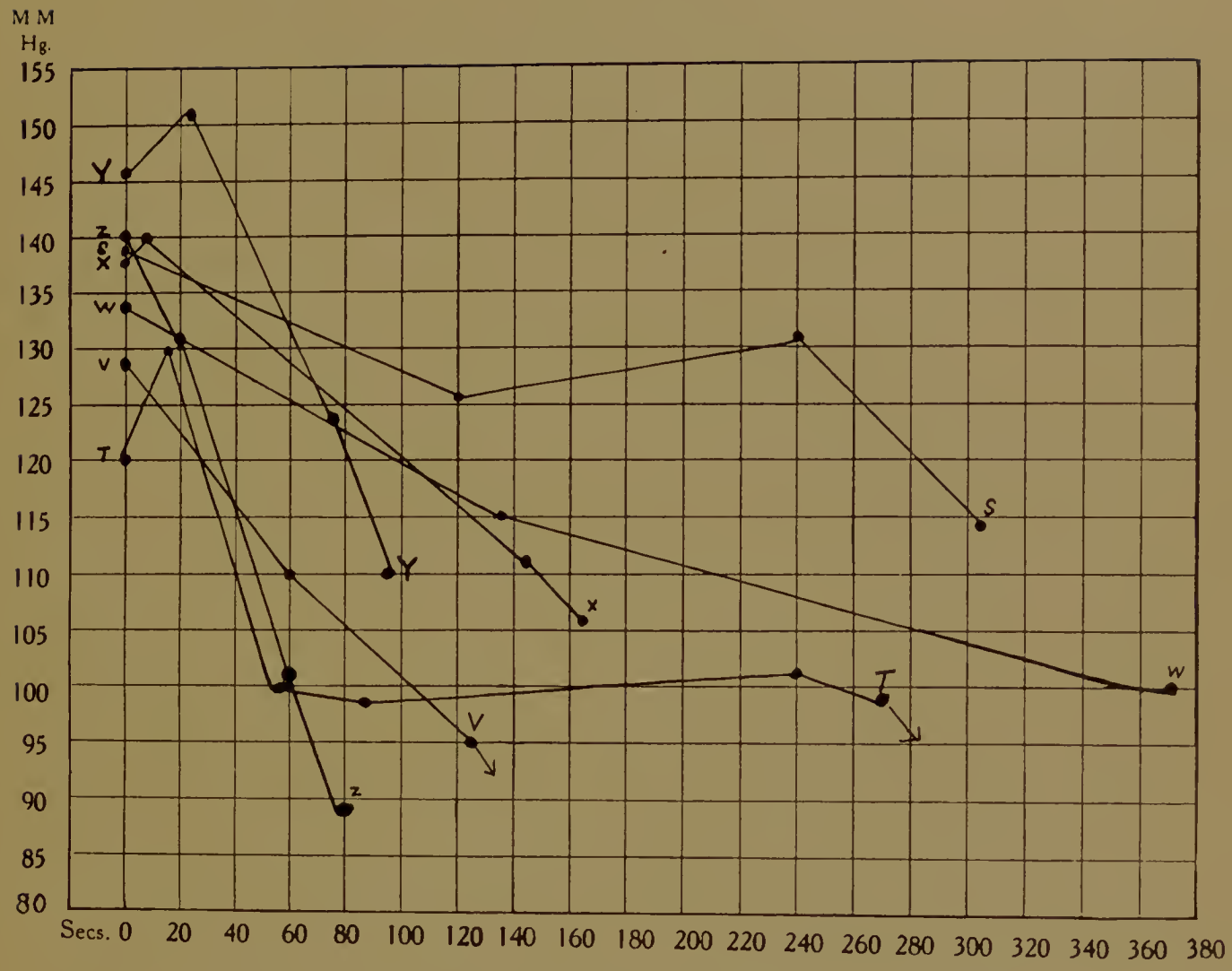
20% ethyl chloride in air given for 60″. (See Record A1).

Heart beats at the beginning of inhalation were 140 per minute, an occasional increased systole occurring. After inhalation for 18″ the stronger systolic contractions of more than twice the normal amplitude appeared every third beat or more. This lasted for 20″, after which, during hyperpnœa, the heart began to fail quickly, becoming irregular and slower (120 per min.) with an amplitude $\frac{2}{3}$ that in the initial and $\frac{1}{4}$ that of the stimulated condition. 20″ after withdrawal of the anaesthetic vapour the irregularity passed off, the beats, although of the same rate, were still small in amplitude. The cardiac beats began to improve before the breathing showed signs of returning. $4\frac{1}{2}'$ after the ethyl chloride was stopped the heart had recovered completely, the amplitude being even greater than before the anaesthetic was administered.

Respiration. Just after the inhalation was begun the respirations were 60 per min. with an occasional deep inspiration. In 20″ hyperpnœa set in, both depth and rapidity quickly increasing till after inhalation for 50″; the rate was 148 per min., the depth being more than doubled. On withdrawal of the anaesthetic the rapidity and amplitude of the respirations rapidly diminished, and 15″ later the breathing ceased, the heart beats only being registered on the stethogram. Complete recovery occurred.

Blood Pressure was = 140 m.m. Hg. at the beginning of the inhalation. On giving the ethyl chloride mixture it began to fall gradually. In 20″ it was = 132 m.m., and with the onset of hyperpnœa its fall was more rapid. When the ethyl chloride was withdrawn at the end of one minute it had fallen to 102 m.m., and continued to fall till 20″ later it reached 88 m.m. From this point it rose gradually. Four times during the fall it suddenly "dipped" about 20 m.m. for 2″ or 3″, viz., 31″ and 43″ after inhalation was begun, and 13″ and 15″ after withdrawal of the anaesthetic. On each of these four occasions, as well as once prior to inhalation, the temporary fall occurred with a temporary arrhythmia of the heart. $4\frac{1}{2}'$ after cessation of the inhalation the B.P. had risen to 144 m.m.

DIAGRAM 1.



EFFECT OF ETHYL CHLORIDE ON BLOOD PRESSURE. EXPERIMENT A.

VAGI INTACT.

Z = 20 % Ethyl Chloride.
Y = 20 % Ethyl Chloride + 10 % CO_2.
X = 20 % Ethyl Chloride + 50 % O_2.
W = 20 % Ethyl Chloride + 50 % O_2.

VAGI CUT.

V = 20 % Ethyl Chloride.
T = 20 % Ethyl Chloride + 10 % CO_2.
S = 20 % Ethyl Chloride + 50 % O_2.

V Whilst drum was stopped there was a fall to 72 m.m. (Time ?). (Drum stopped for 6 minutes).

T After an unknown time a fall to 30 m.m. occurred during the period that the drum was stopped (6 minutes). Artificial respiration was necessary.

20% ethyl chloride + 10% CO_2 in air given for 79″. (See Record A2.)

Heart. At the beginning of inhalation the beats were 140 per min. and strong. In less than 30″ systole began to increase, becoming more so with hyperpnœa. At the height of the hyperpnœa—after inhalation for 45″—the heart beats were 164 per min. with an amplitude nearly doubled. When respiratory paralysis supervened the heart record lost its marked systole, which progressively diminished till an amplitude about normal was reached with a rate of 116 per min. (Respiration by this time was paralysed). Just after the withdrawal of the ethyl chloride the heart became irregular for a few beats, but quickly regained its regularity, and 21″ after the withdrawal and synchronous with the sudden return of good breathing, the cardiac systoles increased again.

Respiration. When the inhalation was started the respirations were 96 per min. For 10″ they were shallow, but they quickly improved, becoming deeper than normal with a rate of 114 per min., and after an inhalation of 30″ hyperpnœa set in, the rate being 156 per min., and the amplitude being double the normal. After an inhalation of 65″ rapid paralysis occurred—the record showing the cardiac pulsations being equal in number to those shown in the cardiogram. 14″ later the bag was removed, and in 22″ the breathing rapidly recovered, the heart at the same time recovering.

Blood Pressure. At the outset of inhalation the B.P. was = 146 m.m. Hg. In 22″ it had risen to 152 m.m., and it kept up well until the heart lost its marked systolic contraction, when it fell, being 124 m.m. when the bag was removed. During the inhalation the B.P. fell temporarily 4 times for 2″ or 3″, the falls varying from 18 m.m. to 24 m.m. 6″ after the inhalation was stopped the B.P. became very irregular synchronous with the irregularity of the heart. 20″ after the bag was withdrawn the B.P. was = 110 m.m., but the lowest point to which it fell was to 88 m.m. during some of the temporary depressions. Return to normal occurred with recovery of the heart and respiration.

20% ethyl chloride + 50% oxygen in air given for 2′ 27″. (See Record A3.)

Heart. The rate was 144 per min., and the beat continued strong, even whilst respiration was almost completely suspended at the beginning of inhalation. Systole increased 50% in 32″ when the respirations became deeper. Rate was unaltered. (The rest of the cardiogram was useless the pointer having loosened).

Respiration. The rate was 90 per min before the administration, and immediately after it was commenced respiration was suspended for 3″ followed by shallow respirations which gradually increased in depth and frequency (165 per min. and somewhat deeper than normal). After inhalation for 1′ 29″ apnœic phases supervened which became more frequent during the remainder of the administration.

Blood Pressure. At the beginning it was 136 m.m. There was an initial rise to 140 m.m. in 6″ followed by a fall which registered 112 m.m. when the bag was withdrawn, and when the drum was stopped 15″ later it had reached 106 m.m. Once during the inhalation (after 1¾′ administration) the pressure fell from 128 to 108 m.m. but returned to 126 m.m. in 5″. (As this fall took place when the cardiograph was at fault the cause is uncertain).

17′ later when the cardiographic pointer was repaired the administration of *20% ethyl chloride + 50% oxygen in air* for 6′ 10″ was repeated. (See Records A4 and 4a).

Heart. The rate, originally 180 per min., was reduced in 2¼′ to 120 per min. with an amplitude increased about 50%. This was followed almost immediately by an increased rate of 162 per min. and an amplitude reduced to normal. This was in turn succeeded by slowing and increased amplitude. The great tendency was, even with these alternations, towards slowing and strengthening of the heart. When the inhalation ceased the rate was 93 per min. with an amplitude slightly greater than normal.

Respiration. The rate was 57 at the outset, but in less than 1′ periods of diminished frequency and force set in and later there were periods of apnœa. Apnœic phases during which the respirations were much slower, 22 per min., alternated with periods of quicker breathing, 46 per min., due most probably to the stimulation of the respiratory centre by the CO_2 generated and retained within the organism during the periods of slower breathing of oxygenated vapour.

Blood Pressure at the beginning of inhalation was 134 m.m. In 2¼′ it had fallen to 115 m.m. and continued to fall gradually so that when inhalation ceased it was 100 m.m., below which it never fell except during temporary depressions, when in each instance the cardiogram, at the corresponding period, showed slight arrhythmia.

Vagi Cut.

At this stage the vagi were cut, and prior to the next experiment the heart rate was 220 per min., respiration 32 per min., and the B.P. = 128 m.m. Hg.

20% ethyl chloride in air given for 2′ 3″. (See Record A5.)

Heart. From 220 per min. it gradually slowed and failed and after inhalation for 1′ the rate was 160 per min. with an amplitude diminished by one half. When the bag was withdrawn the beats were 142 per min. whilst the amplitude was still further reduced.

Respiration was stimulated as regards frequency, for after 1′ inhalation this was increased from 32 to 66 per min. but was shallower. There was a complete absence of the hyperpnœa seen with this mixture when the vagi were intact.

After 1′ 55″, and until the inhalation was stopped, the respiration was almost paralysed, being extremely shallow, and it was impossible to differentiate between cardiac and respiratory waves in the stethogram.

Blood Pressure was lowered considerably, having fallen in 1′ from 128 to 110 m.m. When the inhalation ceased it had further fallen to 95 m.m., and whilst the drum was stopped it fell in an unknown time to 72 m.m.

20% ethyl chloride + 10% CO_2 in air for $4\frac{1}{2}$′. (See Record A6.)

Heart. Prior to inhalation of this mixture the heart rate was 204 per min. With 10″ inhalation of the mixture, slowing to 192 per min. had taken place, and $1\frac{1}{2}$′ later it was down to 162 per min., the amplitude being reduced to a half. $2\frac{1}{2}$′ later, and until after the administration ceased, the rate was unaltered but the heart had weakened, the amplitude being still further diminished.

Respiration rate of 30 per min. prior to administration became somewhat irregular during the first few seconds. This passed off and the rate was 24 per min., and the depth a little increased, but there was a complete absence of the exaggerated breathing seen with the vagi intact. In 1′ it became very irregular, shallow and fast, and paralysis ultimately occurred, necessitating artificial respiration after removal of the bag of anaesthetic vapour. The waves shown in the stethogram are probably cardiac being equal in number to those shown in the cardigram.

Blood Pressure was = 120 m.m. Hg. when inhalation was begun, and there was a rise to 130 m.m. in 15″, and 45″ later it had fallen to 100 m.m. There was but little change during the remainder of the inhalation, being 98 and 102 m.m., but whilst the drum was stopped, after the bag had been withdrawn, it fell to 30 m.m., but the time of the fall cannot be stated.

Artificial respiration having restored the animal

20% ethyl chloride + 50% oxygen in air was given for 5′ 4″. (See Record A7.)

Heart. When inhalation was begun the heart rate was 204 per min. which gradually diminished till after 2′ it was 186 per min. with slightly diminished amplitude. 2′ later the heart became much slower, viz., 168 per min. with an amplitude reduced to $\frac{1}{3}$ of the normal and somewhat irregular.

Respiration, which was 12 per min., as soon as the mixture was inhaled became irregular for a few seconds and then faster and a little deeper (30 per min.) After 2′ the breathing slowed to 24 per min. and only about half the depth. This was followed by respirations which were quicker (60 per min.) and much deeper, this probably being due to the CO_2 generated and retained within the body stimulating the respiratory centre. The slow type of breathing recurred after the administration ceased.

Blood Pressure of 138 m.m. was very gradually reduced to 126 m.m. in 2′, and later when the quicker and deeper breathing set in a rise to 130 m.m. was recorded, after which it fell to 114 m.m.

Recovery of the heart, respiration, and blood pressure had occurred 5′ after the inhalation of the anaesthetic ceased.

Experiment B.—Vagi Cut.

This was performed upon a cat to show the action of ethyl chloride vapour upon respiration and blood pressure with vagi cut.

Normal:—Respirations were 21 per min. and the B.P. = 192 m.m. Hg. (See Record B1.)

The *left* vagus was cut and electrically stimulated with the secondary coil at 10 c.m. B.P. fell from 190 to 164 m.m. On recovery it was stimulated again with the secondary at 10·5 c.m. when the B.P. fell from 194 to 152 m.m.

The *right* vagus was cut and stimulated with the secondary coil at 10·5 c.m. The B.P. fell from 200 to 158 m.m. The respiration when the second vagus was cut became much slower and irregular, viz., 9 per min., and the depth increased to less than double.

15% ethyl chloride in air given for 12′. (See Record B2).

Blood Pressure. When the administration was begun the B.P. = 184 m.m. Hg. and a gradual fall to 166 m.m. in 1′ took place. 2′ later the pressure was 168 m.m., and 1′ later there was a further slight rise to 172 m.m. It had fallen to 160 m.m. in another minute, and 6′ afterwards it was down to 122 m.m., the fall continuing until the inhalation ceased when it was 116 m.m. Thirteen litres of the mixture had been inhaled, i.e., the vapour of 6·5 c.c. ethyl chloride in 12′.

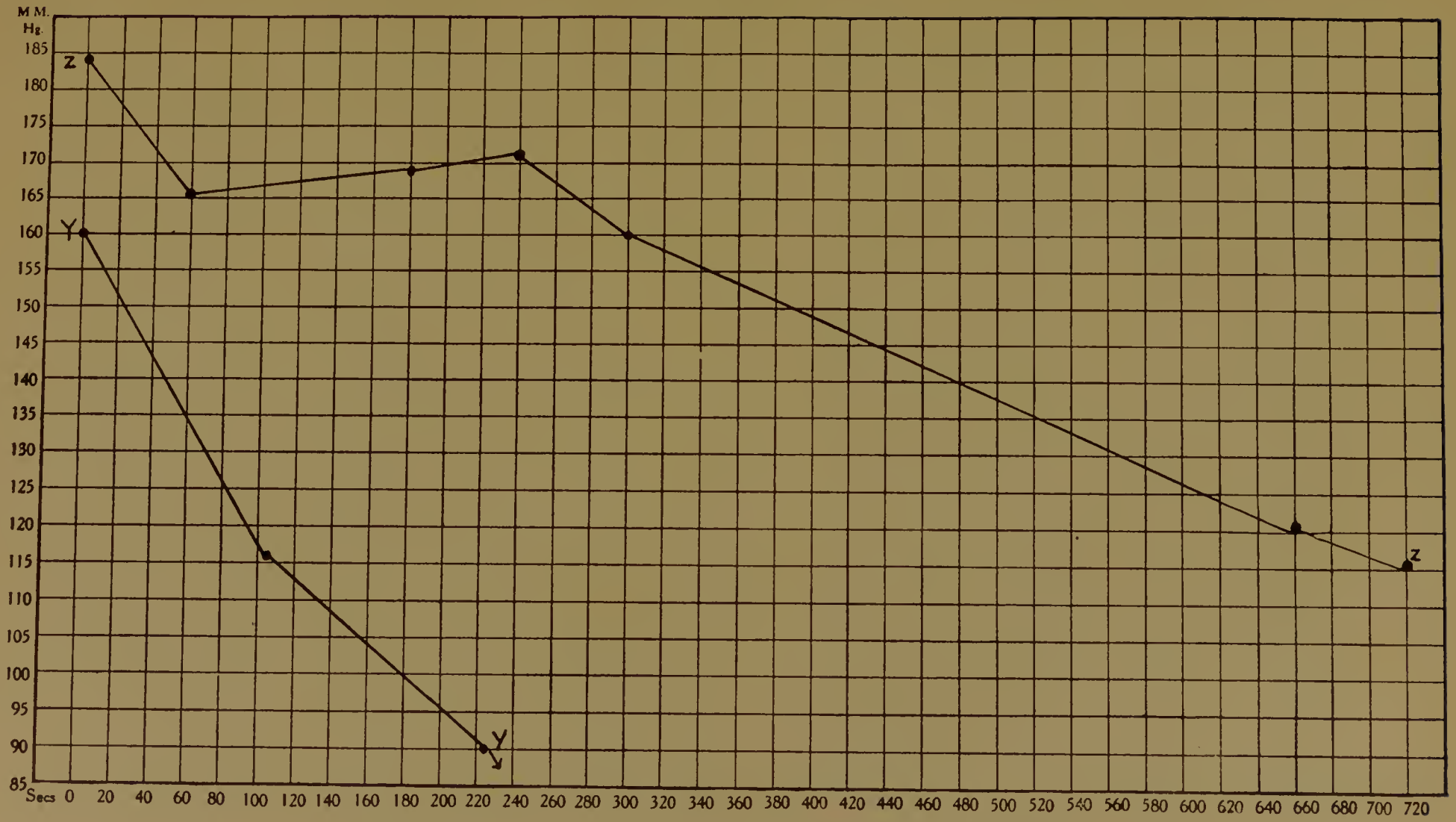
Respiration. The rate was 12 per min. and slightly deeper than normal just prior to inhalation, and when it was conducted it became a little deeper and slower (11 per min.) but it gained gradually in rapidity. 2′ later its rate was 21 per min. and about the normal depth. The breathing became more and more shallow and rapid—42, 60, 100 per min., until on the verge of paralysis when the bag was withdrawn.

After an interval of 5′ during which recovery occurred

20% ethyl chloride in air was given. (See Record B3.)

Blood Pressure, which was 160 m.m., began to fall so that in 108″ it had reached 116 m.m. The left vagus and later the right one were stimulated, the pressure falling in response at once 16 m.m. and 30 m.m. respectively. In $3\frac{3}{4}$′ the B.P. was = 90 m m., and death ensued later. B.P. became irregular when respiration failed. Six litres of mixture were inhaled.

DIAGRAM 2.



EFFECT OF ETHYL CHLORIDE ON BLOOD PRESSURE. EXPERIMENT B.

VAGI CUT.

Z = 15% Ethyl Chloride in air. Y = 20% Ethyl Chloride in air.

Respiration—13 per min. when inhalation was commenced—became at first somewhat slower and deeper, but soon rapidly became more and more shallow until paralysed 2½′ from the beginning of inhalation. Death followed.

Experiment C.

This was upon a cat to show the effect of ethyl chloride upon blood pressure and kidney volume with vagi intact and vagi cut.

Vagi Intact.

10% ethyl chloride in air given for 4¼′. (See Record C1).

Blood Pressure fell in 4″ from 90 to 78 m.m. and in 7″ regained 90 m.m. There was scarcely any further effect during the remainder of the administration, being 89 m.m. at its termination.

Kidney Volume during the inhalation fell a little, which can best be expressed by the height of the tracing from the base line thus :—At the onset of inhalation the tracing was 11·1 c.m. above the base line and at its termination was 10·4 c.m. above it. The fall was very gradual. During an interval both B.P. and K.V. rose

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20% ethyl chloride in air for 2½′. (See Record C2.)

Blood Pressure rose in 12″ from 100 m.m. to 103 m.m. Hg., then fell gradually to 74 m.m. in 1′. A rise followed so that when the administration was concluded B.P. = 84 m.m.

Kidney Volume tracing during the administration fell gradually from 11 c.m. to 10 c.m. above the base line.

After an interval of 14′, the experiment was repeated, the *20% vapour* being administered for 47″.

Blood Pressure was 100 m.m. and in 10″ rose to 110 m.m. from which it gradually fell to 74 m.m. When inhalation ceased the fall continued for 17″ reaching 66 m.m., afterwards rising.

Kidney Volume tracing during the inhalation gradually fell from 11·3 c.m. to 10·4 c.m. above the base line, and when the vapour was withdrawn a further fall to 10·3 c.m. from the base line occurred coincidently with the fall in B.P.

An interval of 4½′ having elapsed with rise in both B.P. and K.V.

25% ethyl chloride in air was given for 4′ 10″. (See Record C2 and 3.)

Blood Pressure initially was = 100 m.m. Hg. A rise to 102 m.m. and a fall to 90 m.m. in 4″ was followed by another rise in 8″ to 100 m.m. From this point a steady fall to 29 m.m. occurred until respiratory paralysis supervened, when the administration was stopped and artificial respiration performed.

Kidney Volume tracing during this experiment fell steadily from 11·4 to 9·5 c.m. above the base line.

Twice during the inhalation the bag containing the anaesthetic mixture was pressed. The first time respiration waves appeared on the B.P. tracing and continued for about a minute after pressure was removed. On the second occasion waves did not appear.

Vagi Cut.

10 % ethyl chloride in air given for 4¾′. (See Record C4.)

The vagi having been cut the above vapour was administered.

Blood Pressure was 136 m.m., but a fall to 93 m m. occurred in 66″ and at this level it remained until the drum was stopped, during which stoppage the pressure fell to zero. Artificial respiration was performed and recovery ensued.

Kidney Volume tracing during this time fell gradually from 10·9 c.m. to 10 c.m. above the base line. The administration was continued for 3¼′ longer whilst the drum was stopped, and during this time the K.V. tracing fell to 8·7 c.m. above the base line.

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20 % ethyl chloride in air for 4′ 42″. (See Record C5.)

Blood Pressure at the outset was 72 m.m. Hg. and rose to 94 m.m. during 17″ whence a gradual fall to 6 m.m. took place. (The amplitude of the heart beats in the B.P. record shows an increase.)

Kidney Volume tracing gradually fell from 11·7 to 9·7 c.m. above the base line in 4′ 15″. At that point the B.P. was 36 m.m., but during the time that B.P. continued to fall the K.V. rose 3 m.m., being 10 c.m. above the base line when artificial respiration was begun.

---

25 % ethyl chloride in air for 4′ 55″. (See Records C6 and 7.)

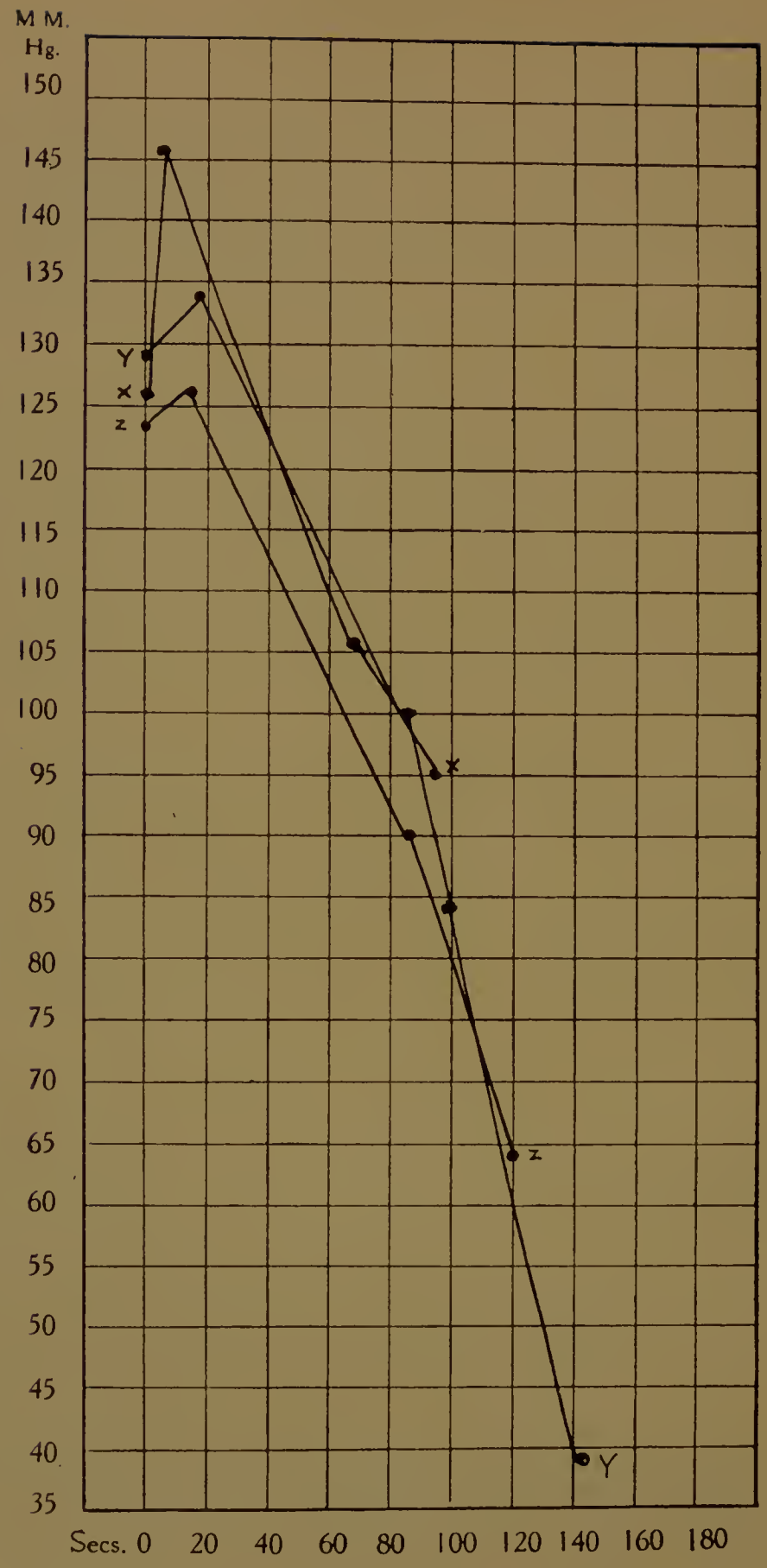
After an interval of 5½′ 25 % E.C. was given.

Blood Pressure was = 84 m.m. Hg. at the beginning and within 15″ it had fallen to 68 m.m. and risen to 92 m.m., from which point it gradually fell to 14 m.m. when the anaesthetic was withdrawn and artificial respiration was begun. The amplitude of the heart beats was increased.

Kidney Volume record was 11·1 c.m. above the base line and a fall gradually took place to 9·4 c.m. a few seconds before the bag was removed. A slight rise of 2 m.m. higher above the base line of the K.V. tracing occurring whilst the B.P. still continued to fall.

Artificial respiration was necessary and fortunately the drum was not stopped. A study of the B.P. and K.V. tracings during, and subsequent to, its performance shows that the cardiac beats were slower and increased in amplitude whilst the B.P. was rising. A slight temporary fall followed stoppage of the artificial

DIAGRAM 3.



EFFECT OF ETHYL CHLORIDE ON BLOOD PRESSURE. EXPERIMENT D.

VAGI INTACT.

Z and Y = 33 % Ethyl Chloride. X = 33 % Ethyl Chloride + 5 % CO_2.

respiration, but gradual recovery ensued. The K.V. tracing shows that when the artificial respiration was begun a further small rise occurred showing respiratory waves, but as the B.P. rose the K.V. tracing began to descend. Very shortly afterwards the K.V. record gradually recovered its normal.

Experiment D. To show the effect upon a dog of E.C. + air and of E.C. + CO_2 + air, also of CO_2 upon respiration and blood pressure. Preliminaries were performed as already described.

33% ethyl chloride in air given for 2′ (?). (See Record D1.)

Blood Pressure was = 123 m.m. Hg. when the inhalation began. It showed a slight initial rise to 127 m.m. but in 20″ it was falling steadily which it continued to do, the descent becoming more rapid with failure of respiration. In 85″ when breathing ceased, B.P. was 90 m.m. and the amplitude of the heart beats in the B.P. tracing was much exaggerated and slower, so that when the bag was removed in 2′ the amplitude was very great, the pressure being = 64 m.m. Hg.

Respiration just after the bag was attached and for 10″ was slightly irregular but regularity returned and the rate was 57 per min. Stimulation in depth and rate followed, viz., 78 per min. and depth trebled. In 1′ breathing began to fail, and 38″ later it was paralysed, showing only a few slight gasps at intervals. 20″ later the bag was removed and artificial respiration resulted in recovery. The chest, as respiratory failure developed, assumed a position of expiration, the lever having gradually risen to a higher level than it had done in the expiration stroke during the early stage of the administration.

On recovery, the same mixture was re-administered with identical results. (See Records D1 and 2.) :—

The *Blood Pressure* tracing showed a slight initial rise (from 129 m.m. to 133 m.m.) and then a steady fall until in 85″, when breathing ceased, B.P. had fallen to 100 m.m. At this point Ringer's Solution, saturated with CO_2, was injected intravenously, but B.P. continued to fall and the bag was removed 10″ later B.P. being 84 m.m. The fall continued until 48″ later, being = 39 m.m., artificial respiration was employed with a successful result.

Respiration prior to inhalation had a rate of 106 per min. When the bag of vapour was attached it became irregular and slower, 36 per min., but in about ½′ regularity and a greater rapidity obtained, followed in a few seconds by some hyperpnœa—160 per min. with the amplitude doubled. Rapid respiratory paralysis supervened, absolute cessation of breathing occurring 85″ after attachment of the bag. Intravenous injection of Ringer's Solution, saturated with CO_2, had no effect upon breathing, but artificial respiration, started about ¾′ after breathing had ceased, was followed by complete though slow recovery.

Effect of CO_2. (See Records D2 and 3.)

After recovery, the effect of CO_2 was tried by giving the gas through a catheter passed into the trachea and allowing a slow stream to be inhaled for 15″. When fourteen respirations had been performed hyperpnœa occurred, the breathing becoming much deeper and slower. The stimulation lasted for about a minute after the withdrawal of the CO_2 and gradually passed off. Repetition of the inhalation 2′ later for 15″ produced a similar result, the breathing becoming more hyperpnœic and slower than during the previous inhalation of CO_2. The stimulation passed off more quickly. The effect upon the blood pressure of CO_2 was a slight fall at the beginning of hyperpnœa on both occasions followed by a rise.

33 % ethyl chloride + 5 % CO_2 in air given for 73″. (See Record D3).

Blood Pressure was = 126 m.m. Hg. just before inhalation and began to rise, reaching, in 5″, 146 m.m. This was followed by a steady fall until it was 107 m.m. when the inhalation was discontinued. With the progressive respiratory paralysis which followed removal of the bag the fall in B.P. continued so that when complete cessation of breathing occurred 23″ later it had dropped to 95 m.m. With artificial respiration it rose gradually until the pressure was = 103 m.m The breathing was stimulated with CO_2 passed through the tracheal tube for 40″ causing at first a slight rise in B.P., but as the breathing deepened the pressure dropped, registering 77 m.m. on withdrawal of the gas.

Respiration, just prior to inhalation, had a rate of 60 per min., and immediately on inspiring the anaesthetic mixture this deepened and quickened—87 per min.—with double the amplitude in 68″. Paralysis quickly supervened with the chest in the expiratory position. Artificial respiration was performed for about 40″, recovery being slow. One minute later CO_2, through the tracheal tube, was given for 43″, resulting in rapid recovery with hyperpnœa.

Experiment E. This was performed on a cat to show the effect of E.C. + O_2, E.C. + CO_2 + air and E.C. + air, upon respiration and blood pressure. The preparations were as already detailed, and this animal received a dose of morphia as well as ether.

15 % ethyl chloride + oxygen given for 3′. (See Record E1.)

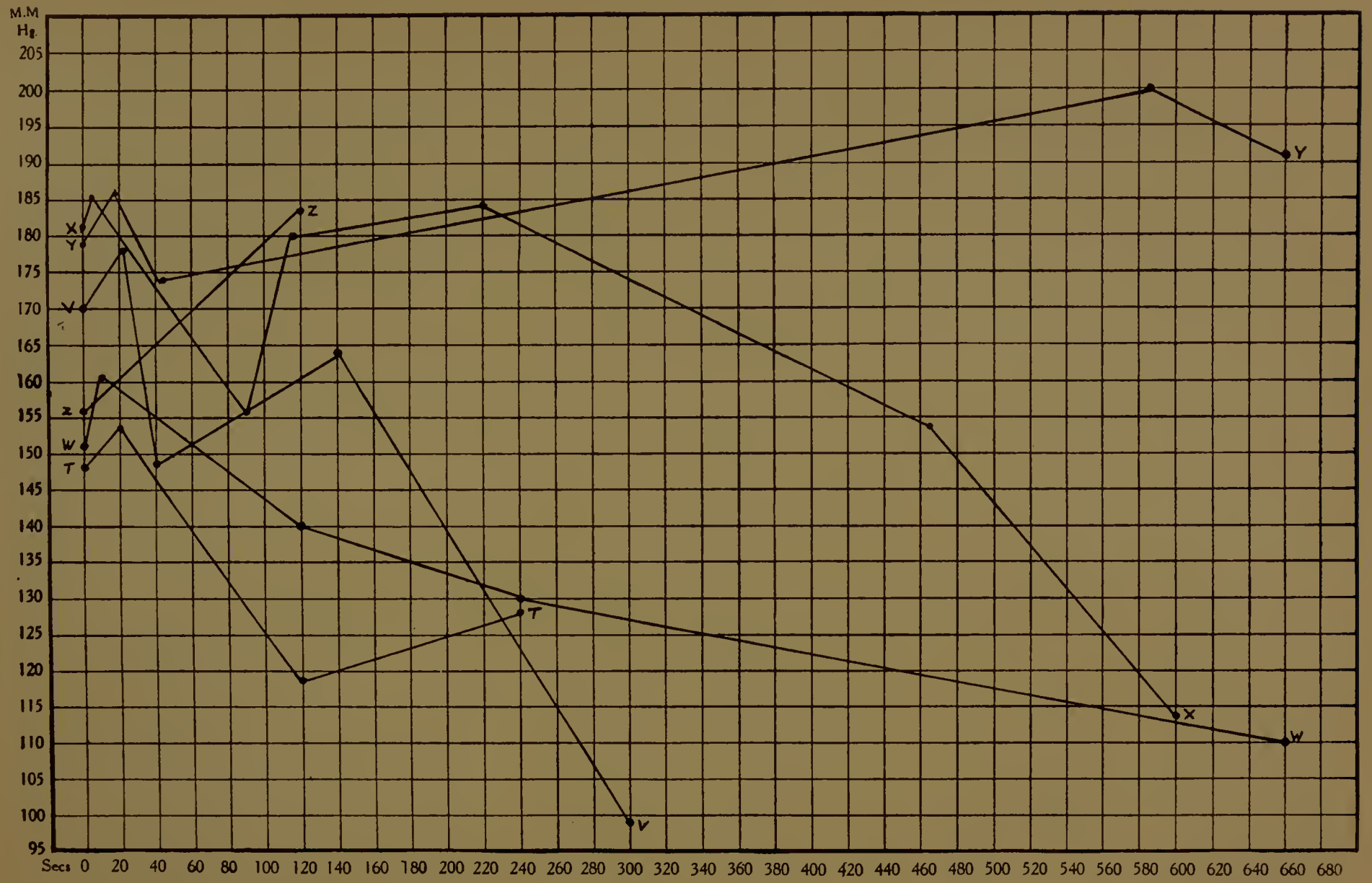
Blood Pressure was = 156 m.m., at which it remained until in 2′ it began to rise, reaching 183 m.m. The rise was synchronous with slower and shallower breathing.

Respiration—21 per min.—diminished in depth and frequency due no doubt to the oxygen inhaled.

(This experiment was stopped because of a clot having formed in the canula.)

The experiment was repeated with the above mixture for 11′. (See Record E2.)

DIAGRAM 4.



ACTION OF *Oxygen* AND OF *Carbonic Acid* UPON THE EFFECT OF ETHYL CHLORIDE ON BLOOD PRESSURE. EXPERIMENT E. VAGI INTACT.

Z = Ethyl Chloride 15 % in O_2 (Imperfect from clot in canula).
Y = Ethyl Chloride 15 % in O_2.
X = Ethyl Chloride 15 % in O_2.
W = 15 % Ethyl Chloride + 10 % CO_2.
V = 20 % Ethyl Chloride + 10 % CO_2.
T = 20 % Ethyl Chloride.

Blood Pressure as the inhalation was started was = 178 m.m. Hg. There was a slight rise to 186 m.m. and a fall to 174 m.m. within 42″ of the application of the bag to the inspiratory tube. Then followed a continuous rise to 200 m.m. in 10′, and when the anaesthetic was withdrawn 1′ later the tracing registered 193 m.m.

Respiration slowed in 2′ from 22 to 13 per min., being also shallower. At the end of the administration the breathing was very rapid and shallow.

20% ethyl chloride in oxygen given for over 10′. (See Records E3 and 4.)

Blood Pressure rose slightly—from 180 to 186 m.m.—in 6″ but fell gradually to 156 m.m. in 95″. This fall was coincident with slowed breathing, but as the respiration became faster, again the B.P. rose to 180 m.m., and after an inhalation of 3′ 40″ registered 184 m.m. After an inhalation of $3\frac{3}{4}$′ the drum was stopped, and on its resumption 4′ later the pressure had fallen to 148 m.m., and a further fall occurred till the inhalation was stopped, when it had reached 114 m.m. The anaesthetic having been removed it rose, and when registering 154 m.m. the right vagus was stimulated (secondary coil at 5 c.m.) when an immediate fall to 114 m.m. resulted, followed by a rapid rise to 180 m.m.

Respiration slowed from 14 to 12 per min. and became shallower after inhalation for 30″. $1\frac{1}{2}$′ later it was more rapid and shallow, being 22 and later 44 per min. It was slower and a little deeper when the bag was removed. Gradual recovery took place.

15% ethyl chloride + 10% CO_2 in air given for 11′. (See Record E5.)

Blood Pressure with this mixture rose in 10″ from 152 m.m. to 162 m.m., this being maintained for about 30″ when a gradual fall set in reaching, in 2′, 140 m.m. 2′ later it was down to 130 m.m., and when the bag was removed it was 110 m.m.

Respiration in 2′ increased from 14 to 16 per min. 2′ later breathing had almost ceased, but the respirations became gradually a little stronger and very rapid (60 per min.) after an inhalation of 6′. At the end of the administration they numbered 66 per min. As the tambour was inflated nearly 5′ before the termination of the experiment a comparison of the depth of breathing is impossible.

20% ethyl chloride + 10% CO_2 in air given for 45″ and later for 5′. (See Record E6.)

Blood Pressure. On attachment of the bag of mixture the pressure rose in 10″ from 170 m.m. to 174 m.m., and then fell so that when the administration ceased it was 138 m.m.

Respiration. The rate was 15 per min. just prior to administration, and breathing became slower and shallower.

Two minutes later the experiment was repeated, the inhalation lasting 5′.

Blood Pressure. In 25″ this had risen from 168 m.m. to 178 m.m. A fall set in, and in about 15″ it had reached 148 m.m., but this was followed by a rise to 164 m.m. and another fall to 98 m.m. by the time the anaesthetic was withdrawn. Recovery to 150 m.m. occurred during an interval of 5′.

Respiration. The rate at beginning of inhalation was 18 per min., becoming first slower (15 per min.), then more rapid and less deep, so that after inhaling for 140″ the rate was 54 per min., and when the bag was withdrawn breathing had a rate of 64 per min., the depth being half the normal.

On recovery,

20% ethyl chloride in air was given for 4′. (See Record E7.)

Blood Pressure was = 148 m.m. Hg. at beginning of inhalation. In 20″ there was a slight rise to 154 m.m., then a gradual fall which registered 118 m.m. in 2′. When administration ceased, 2′ later, the pressure had risen to 128 m.m.

Respiration rate was 15 per min., as inhalation was begun, and after four shallower and slower breaths it became quicker. In 2′ the rate was 18, and at the end of administration 48 per min. and very shallow.

Experiment F. Ventricle Plethysmograph.

The method employed is that described in page 9, except that a bellows recorder was used instead of a tambour. The systolic contraction is recorded in the upstroke. A cat was used for this experiment in the first part of which the vagi were intact, and in the later they were cut.

Vagi Intact.

15% ethyl chloride in air given for 2′. (See Record F1.)

When the heart was placed in the plethysmograph the tracing showed strong beats at the rate of 105 per min.

Nearly 5′ later the bag containing the above mixture was attached to the inspiratory limb of the tracheal tube. The rate was then 96 per min. After an inhalation of 38″ the heart showed decided stimulation, the systole having greatly strengthened. The anaesthetic was withdrawn in 2′ when the diastolic stroke was recorded at a much lower level upon the paper, and the systolic stroke had diminished in amplitude. The rate was unaltered.

About 9′ later

20% ethyl chloride in air was given for $6\frac{1}{2}$′.

The heart beats were strong and 93 per min. when the anaesthetic was given,

and no alteration in rapidity or strength had occurred when the drum was stopped in 27″. When it was started after an interval of 6′, and 13″ before withdrawal of the anaesthetic, the diastolic stroke was again recorded at a low level, and the amplitude of the systole was reduced to about $\frac{3}{5}$ of that at the beginning of inhalation, whilst the rate was increased to 108 per min.

Vagi Cut.

After cutting the vagi the heart quickened, but before administering the anaesthetic it had slowed down to 96 per min.

15 % ethyl chloride in air was then given for 6′ 27″. (See Record F2.)

After inhalation for 6′ the drum was started, and again the diastolic strokes had attained a lower level, whilst the amplitude of the systole had diminished to almost half. The rate was a little quicker, viz., 99 per min. 3′ later the heart had returned to normal. Lest the alteration in the cardiac beats might be due to the fact that the vapour was being inhaled from an enclosed space, and not to the anaesthetic vapour, air only was administered for 2′ 34″ as a *control experiment.* The same bag as had contained the anaesthetic vapour was filled with air and attached to the inspiratory limb of the tracheal tube. No alteration whatever in the amplitude or rate of the beats resulted, nor were the diastolic strokes recorded at a lower level.

The next experiment was conducted with

15 % ethyl chloride + 46·6 % oxygen in air for 6½′. (See Record F2.)

After the inhalation was started the rate was 114 per min., the amplitude being about equal to that obtained during the control experiment. At the completion of the administration the amplitude had fallen to about $\frac{2}{3}$ of the normal, and the diastolic stroke registered at the low level. The rate was practically unaltered. Recovery ensued on breathing pure air.

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15 % ethyl chloride in pure oxygen was next given for 6′ 40″. (See Record F2.)

The result obtained was that after 6′ the rate was increased from 102 to 120 per min., whilst the amplitude was diminished to half, and the diastolic stroke was again lowered.

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15 % ethyl chloride + 6·6 % CO_2 in air was given for 6′ 13″. (See Record F3.)

Prior to administration of this mixture the rate was 80 per min., whereas after an inhalation of 6′ the rate had but slightly increased—to 88 per min.—and the amplitude had diminished to a half with the diastolic stroke recorded at a lower level. The gradual loss of the lowered diastolic stroke of the lever is well shown in the recovery record.

Experiment L.

This experiment, to demonstrate the effect of ethyl chloride upon the heart, was performed with a needle passed into the heart as described upon page 9.

The animal used was a cat, with the vagi first intact and afterwards cut.

(The early part of the experiment, during which three inhalations had been given—15%, 20%, and 20% respectively—was useless from leakage of the tambour. After repair the following results were obtained.)

Vagi Intact.

25% ethyl chloride in air was given for 1′. (See Record L.)

Just before the vapour was given the heart beats were 160 per min., and after an inhalation of 47″ the beats had slowed down to 70 per min. with the amplitude reduced to less than half. On removal of the anaesthetic the failure increased, the beat being almost entirely lost. Recovery occurred with artificial respiration, the rate being 116 per min.

After an interval of 5′,

30% ethyl chloride in air was given for 2′ 55″,

The beats increased from 140 to 160 per min. with a slightly diminished amplitude. The heart gradually failed, and after 2′ 40″ the rate was 65 per min. and almost paralysed. Recovery resulted with artificial respiration.

Vagi Cut.

The vagi were cut, and it will be seen on comparing the four beats prior to, with those after, section that a restraining influence on the heart was dispelled. The cardiac rate was 160 when

25% ethyl chloride was given for 2′.

No paralytic effect was demonstrated, and 5′ later

30% vapour was administered. 4½′ later, the heart was not seriously affected although the amplitude was diminished.

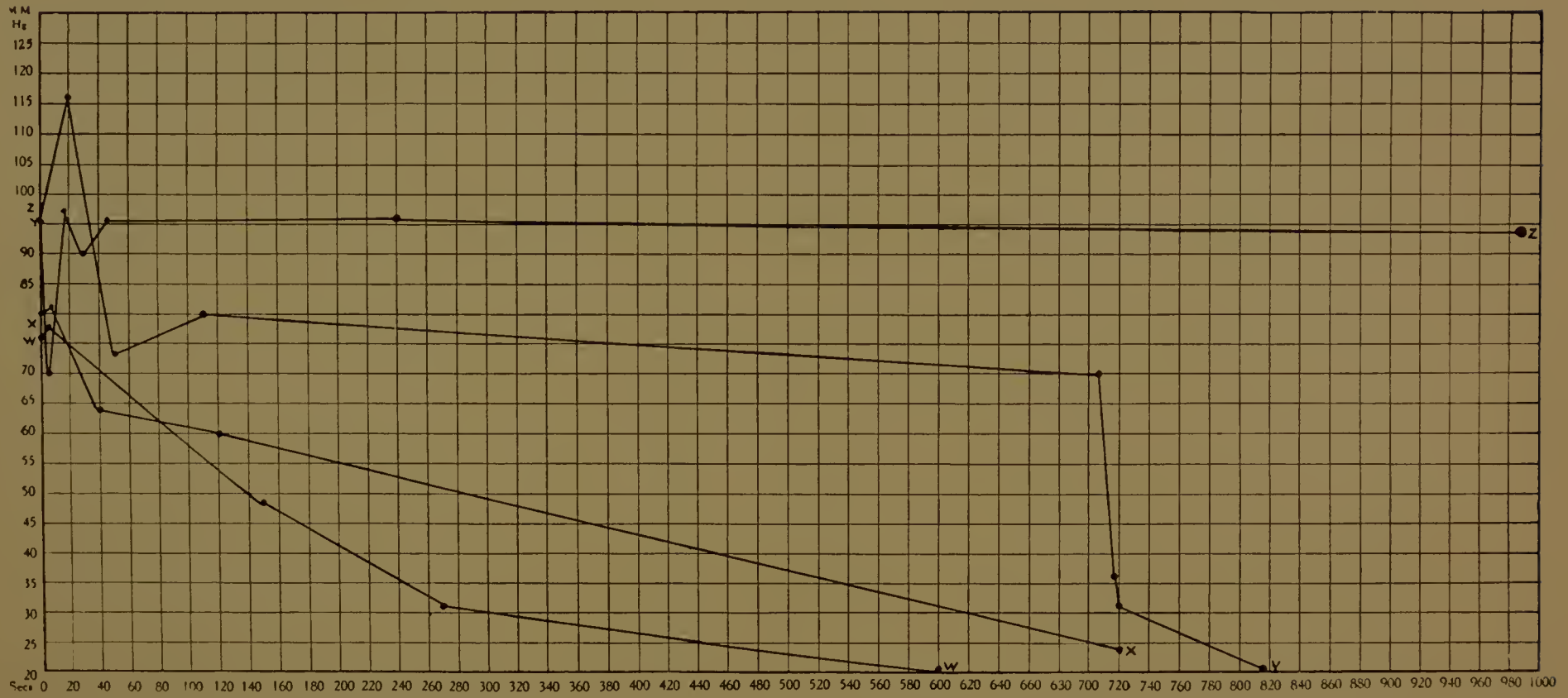
Experiment M. This was done to show any difference in the effect produced, by ethyl chloride, upon the auricles and ventricles respectively. The method and apparatus employed are described on page 10. The animal used was a cat. (See Records M1 and 2.)

The normal ventricular beats were 170 per min. and the amplitude 2·5 m.m., whilst the auricular beats were 170 per min. with an amplitude of 5·5 m.m.

6·6% ethyl chloride in air was given.

In ½′ there was sudden weakening of the ventricular beat, and in 3′ its

DIAGRAM 5.



EFFECT OF ETHYL CHLORIDE ON BLOOD PRESSURE. VAGI INTACT. EXPERIMENT N.

Ethyl Chloride in Air and Ethyl Chloride + CO_2 in Air.

Z = 5 % Ethyl Chloride. Y = 10 % Ethyl Chloride. X = 10 % Ethyl Chloride. W = 10 % Ethyl Chloride + 2·5 CO_2.

amplitude was reduced to 20 % of the normal. The auricular beat was not altered in rate but the amplitude was diminished to 63·5 % of the normal. The ventricles therefore were affected about three times as severely as the auricles. When the inhalation was stopped both auricles and ventricles recovered. Further inhalation of the same strength of vapour again caused diminished amplitude of the beats, but in this instance the auricular record was the more affected. The ventricular tracing, just prior to inhalation, showed an amplitude which gradually lessened, till after an inhalation of 4′ 30″ it was reduced to 50 %. The auricular tracing, on the other hand, showed a gradually diminished amplitude which, at the end of the administration, was reduced to 40 %. Recovery ensued upon breathing of pure air.

Experiment N. This was performed to demonstrate the effect of E.C. + air and of E.C. + CO_2 + air upon respiration and B.P. with vagi intact. The animal used was a cat, and the preliminary preparations with tracheal tube and carotid canula were as already described on page 9.

5 % ethyl chloride in air was given for 16½′. (See Record N1.)

Blood Pressure, when inhalation of this vapour was begun, was 98 m.m. The vapour issued from the bag with some force on being attached to the tracheal tube, causing irregularity of respiration, and this was accompanied by a fall of B.P. in 8″ to 70 m.m., but had returned to 97 m.m. 8″ later. In 30″ it had fallen to 90 m.m., and 18″ later it was 96 m.m. —a level which was about maintained throughout—for in 4′ it was 97 m.m. and after inhalation for 16½′ it registered 94 m.m.

Respiration normally was 22 per min. and deep. Just as the bag containing the anaesthetic was applied to the tracheal tube the vapour escaped with some force, causing irregularity of breathing, but it recovered in about 20″. When 11 normal respirations had been taken the breathing became shallow but unaltered in rate. This lasted only 1′, when the respirations increased in depth, but a little slower, becoming deeper and faster towards the end of inhalation. On removal of the bag, breathing was deeper than normal and the rate was 24 per min.

After an interval of a few minutes,

10 % ethyl chloride in air was given for 12′. (See Record N2.)

Blood Pressure as the inhalation began was = 96 m.m. Hg., but in 20″ had risen to 117 m.m. 30″ later it had fallen to 74 m.m. synchronous with the more rapid breathing. It rose 1′ later to 80 m.m. After inhalation for 11¾′ it had fallen to 70 m.m., and 7″ later it had dropped rapidly to 36 m.m. 8″ later, when the bag was removed, it had fallen to 32 m.m., respiration being still deep and rapid. The breathing remained deep for 56″ after the fall in B.P., 37 inspirations being taken in that time. After this the breathing became more and more shallow,

ceasing altogether in about 20″. 30″ after cessation of breathing B.P. registered only 20 m.m., but with artificial respiration complete recovery ensued.

Respirations, just prior to administration, had a rate of 21 per min. and were deep (the animal moved as the inhalation began and is the explanation of the early irregular breathing). On inhaling the vapour the breathing became very shallow—about $\frac{1}{5}$ the normal amplitude—for 6 respirations, but increased in depth and frequency. Very soon the breathing improved, and as the depth increased and approached normal it slowed down to the normal rate, the respiration waves showing better in the B.P. tracing than earlier. After an inhalation of 9′ the breathing was still as deep but much faster (38 per min.), and just before the fall of B.P. it was 46 per min. For 56″ after the B.P. fell 37 inspirations were taken, but quickly became more shallow and finally ceased altogether. Half a minute later artificial respiration was performed and recovery occurred.

The experiment with *10% E.C.* was again performed. The administration lasting 12′. (See Record N3.)

Blood Pressure rose in 10″ very slightly (from 80 to 82 m.m.), but fell gradually, so that 30″ later it was 64 m.m. After a further period of 80″ B.P. had fallen to 60 m.m., and 10′ afterwards, when the inhalation was stopped, it had fallen to 24 m.m. Recovery occurred with artificial respiration.

Respiration. The rate as inhalation was begun was 20 per min., and after 2′ it had slowed a little (18 per min.) and diminished about $\frac{1}{5}$ in amplitude. After administration for 11′ respiratory failure set in, and complete paralysis occurred, necessitating artificial respiration which restored the animal.

10% ethyl chloride + 2·5% CO_2 in air given for 10′. (See Record N4.)

Blood Pressure was = 76 m.m. Hg., and after a slight preliminary rise to 78 m.m. immediately began to fall, reaching 48 m.m. in $2\frac{1}{2}$′. After a further 2′ it had fallen to 32 m.m., and when the inhalation was stopped it had reached 20 m.m.

Respiration was very slow (16 per min.) and deep before the mixture was given, and became a little shallower and quicker at once, deepening and quickening after a few breaths, but as the inhalation proceeded it gradually became more and more shallow = about $\frac{1}{2}$ that registered before the anaesthetic was administered. After 7′ breathing had quickened to 22 per min. and diminished in depth. 9′ after the bag had been attached complete paralysis ensued, recovery occurring with artificial respiration, which was begun on removal of the bag which had been applied for 10′.

DIAGRAM 6.

EFFECT OF ETHYL CHLORIDE ON BLOOD PRESSURE. VAGI INTACT. EXPERIMENT O.

Z = 7·5 % Ethyl Chloride. Y = 15 % Ethyl Chloride.

Experiment O. This experiment upon a cat was performed to show the effect of ethyl chloride in various strengths upon respiration and blood pressure. The method and apparatus employed is described upon page 9.

7·5 % ethyl chloride in air given for 14′. (See Record O1.)

Blood Pressure was normally = 156 m.m. Hg. In 5″ it had risen to 160 m.m., and 10″ later it was down to 146 m.m. The fall continued gradually until in 4½′ it had reached 114 m.m. From this point it gradually rose, and 8′ after the attachment of the bag it had gone up to 136 m.m. Here a small temporary depression occurred, followed by a further rise in 45″ to 148 m.m., and when the administration ceased it was up to 152 m.m. The experiment was stopped because the bag (18 litres) was exhausted.

Respiration was very rapid in this animal, having a rate of 230 per min. with good amplitude. At the beginning of inhalation it became deeper and somewhat slower. This hyperpnœa was followed by shallower respirations, but which had an amplitude greater than the normal as well as being slower (84 per min.) In 1′ breathing was about normal, both in rate and depth, and were succeeded in 2½′ by slower and deeper respiration. This series of changes occupied about 4½′, and 2′ later breathing was again shallower and rapid. From this point for the next 7′ the alteration in depth to 30 % above normal and in frequency to 78 per min. was gradual until the administration ceased with emptying of the bag.

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15 % ethyl chloride in air given for 8½′. (See Record O2.)

Blood Pressure at the outset was = 122 m.m. Hg. An initial rise to 126 m.m. and fall to 110 m.m. in 15″ was followed by a gradual fall during a further 2′ to 102 m.m. From this point it rose, reaching 148 m.m. in 40″. In 4′ from the attachment of the bag it was 140 m.m. 4′ later it had fallen to 64 m.m., and when the anaesthetic was withdrawn ½′ later B.P. had been reduced to 16 m.m., respiration having failed. A few seconds after the removal of the bag the B.P. tracing showed complete absence of heart beats, which returned after artificial respiration had been energetically performed and B.P. began to rise.

Respiration, prior to giving this mixture, had the rapidity and depth of the normal animal, but as soon as the vapour was inhaled a decided change occurred. With the inhalation of the vapour shallow respiration was carried on with the chest in a position of expiration, the recording point being maintained at a higher level than its normal expiratory position. In 6″ the animal took a very deep inspiration (3 times the depth of the normal), but the lever returned at once to its expiratory position with the respirations about half the normal depth. This type of breathing with the chest in the expiratory position gradually passed off, the lever dropping to normal, the amplitude also increasing to normal, but as it did so the breathing became much slower (54 per min.), and in about 2½′ marked arrhythmia set in followed in 6′ by paralysis. Energetic artificial respiration slowly restored the animal.

9 litres of vapour were inhaled during the experiment.

EFFECTS OF ETHYL CHLORIDE ON BLOOD PRESSURE.

The experiments upon the effects of E.C. upon B.P. were conducted to discover—

(1.) The influence of various percentages of E.C. vapour.

(2.) The effect of mixing oxygen with the anaesthetic.

(3.) The effect of mixing CO_2 with the anaesthetic.

THE EFFECT OF VARIOUS PERCENTAGES OF ETHYL CHLORIDE.

The experiments bearing upon this are as follows :—

5 % experiment N.
7·5 % ,, O.
10 % ,, N.
15 % ,, O ; with vagi cut, B.
20 % experiments A and E ; with vagi cut, A and B.
33 % experiment D.

5 % ethyl chloride vapour in air. (See Record N1, diagram 5, and notes, page 25.)

It will be seen that at the outset the pressure registered 98 m.m. of Hg., and in less than 70″ it had fallen to 70 m.m., risen to 97 m.m., fallen again to 90 and again risen to 96 m.m. The cause of this is to be found in the notes, namely, that on attaching the distended bag the vapour was allowed to escape with force through the inspiratory valve, and cause marked irregularity of breathing. This condition of the breathing is well shown in the record. When once the pressure was righted, B.P. kept up so that after an inhalation of 16½′ the pressure registered 94 m.m.

The conclusion may be arrived at—that a 5 % vapour can be given for a prolonged period without lowering B.P.

7·5 % ethyl chloride vapour in air. (See Record O1, diagram 6, and notes, page 27.)

Examination of these will show that the normal B.P. was = 156 m.m. of Hg. A slight preliminary rise to 160 m.m. occurred, followed by a sharp fall within 20″ to 145 m.m. Then a gradual fall to 114 m.m., after an inhalation of 4½′. From this point the pressure gradually rose, and 4¼′ later it reached 148 m.m., a further slight rise occurring, so that after an administration of 14′ it had risen to 152 m.m.—practically its original level.

This experiment would seem to point to the fact that, after a slight initial rise, a 7·5 % E.C. vapour in air causes a lowering at first, but that the organism soon adapts itself to this strength of vapour, with complete recovery during a fairly prolonged administration.

10% ethyl chloride vapour in air. (See Records N2 and 3, diagram 5, and notes, page 25.)

Two experiments were conducted with 10% E.C. vapour in air.

In the former the B.P. stood at 96 m.m. when inhalation was begun In 20″ it had risen to 117 m.m., but had dropped to 74 m.m. 20″ later. Here a rise occurred, so that in 1′ it had reached 80 m.m. From this point a steady gradual fall to 70 m.m. occurred, taking almost 10′ in its descent. From this point it rapidly fell, reaching 32 m.m. in 8″. The fall continued to 20 m.m. after withdrawal of the anaesthetic, and recovery only occurred with artificial respiration.

This experiment was repeated, and at the commencement of inhalation the B.P. was 80 m.m. Upon inhalation of the mixture a very slight rise occurred (to 82 m.m. in 10″), but it immediately fell, reaching 64 m.m. with an inhalation of 40″. The descent continued; in 80″ it was down to 60 m.m., and when the inhalation ceased it had reached 24 m.m. Again artificial respiration aided recovery. The administration in both experiments was of the same duration.

From these experiments it may be gathered that 10% vapour is of sufficient strength to cause a preliminary decided rise of B.P., and that the subsequent fall is such as to still maintain a good and safe pressure unless administration of vapour of this concentration is prolonged for several minutes. Also that after recovery renewed administration of vapour of this concentration is such as almost immediately to cause a continual fall requiring restorative measures.

A 10% E.C. vapour is safe for short administration, but dangerous for more prolonged administration, but recovery can be obtained by restorative measures.

15% ethyl chloride vapour in air (See Record O2, diagram 6, and notes, page 27.)

When 15% E.C. vapour in air was begun the B.P. was = 122 m.m. Hg. A slight rise in 5″ to 126 m.m. was followed by a fall to 110 m.m. after an administration of 15″. A further slight fall occurred, so that after an inhalation of $2\frac{1}{4}$′ it was = 102 m.m. A rise followed, and in 40″ it was 148 m.m. when a steady continuous fall occurred. 65″ later it had fallen to 140 m.m., and a further steady fall occurred, so that 4′ later it had dropped to 64 m.m., and 30″ later it was = 16 m.m. This experiment is interesting and instructive, being the only one in the whole series in which the heart beats disappeared from the B.P. record when the pressure reached its minimum, and shows that with energetic artificial respiration the beats gradually were restored to the tracing with recovery of the animal.

This experiment shows that with a 15% vapour the B.P. is well maintained at first, but that later a profound and rapid fall occurs which can be recovered by prompt and a considerable period of artificial respiration. This experiment also demonstrates that recovery may occur even after the heart has ceased beating.

15 % ethyl chloride in air with vagi cut. (See Record B2, diagram 2, and notes, page 16.)

A B.P. of 184 m.m. fell in 1′ to 166 m.m., a slight rise in 2′ to 168, and another in 1′ to 172 m.m. followed. 1′ later it had fallen to 160 m.m., and 6′ later to 122 m.m., and when an inhalation of 12′ was stopped the B.P. was reduced still further to 116 m.m.

Comparing this with the preceding, in which the vagi were intact, we see that the administration was more prolonged, and there was not the rapid fall in B.P. after some minutes administration. This may be due either to the fact that an impulse generated in the centre was not capable of being conducted to the heart, or that the respiration being slower and shallower the amount of E.C. vapour inhaled was very much less, and so produced a decidedly less effect upon the heart muscle. In the light of other experiments the latter is probably the correct view, and goes to prove that a vapour of 15 °/₀, if inhaled with slow and shallow breaths, will not seriously disturb the cardiac strength even after several minutes inhalation.

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20 °/₀ ethyl chloride vapour in air. (See Records A1 and E7, diagrams 1 and 4, and notes, pages 12 and 22.)

A1. The B.P. in this experiment, with 20 °/₀ E.C. vapour in air, shows no rise, but a constant fall. At the outset it was = 140 m.m. Hg., in 20″ it had fallen to 132 m.m., and in 40″ more, when the anaesthetic was withdrawn (i.e., after an administration of 1′), it had fallen to 102 m.m. and continued to fall, being = 88 m.m. 20″ after the withdrawal of the anaesthetic. Four "dips" during the fall were synchronous with some arrhythmia of the heart.

E7. This experiment was performed upon an animal (a cat) to which 5 inhalations had already been given, viz., 15 °/₀ E.C. in O_2, 15 °/₀ E.C. in O_2, 20 °/₀ E.C. in O_2, 15 °/₀ E.C. + 10 °/₀ CO_2 in air, and 20 °/₀ E.C. + 10 °/₀ CO_2 in air.

On beginning the inhalation of 20 °/₀ E.C. in air the B.P. = 148 m.m., and the first effect was a slight rise to 154 m.m. in 20″, this was followed by a gradual fall so that in 2′ it was down to 118 m.m. 2′ later, when the anaesthetic was withdrawn, it had risen a little (to 128 m.m.)

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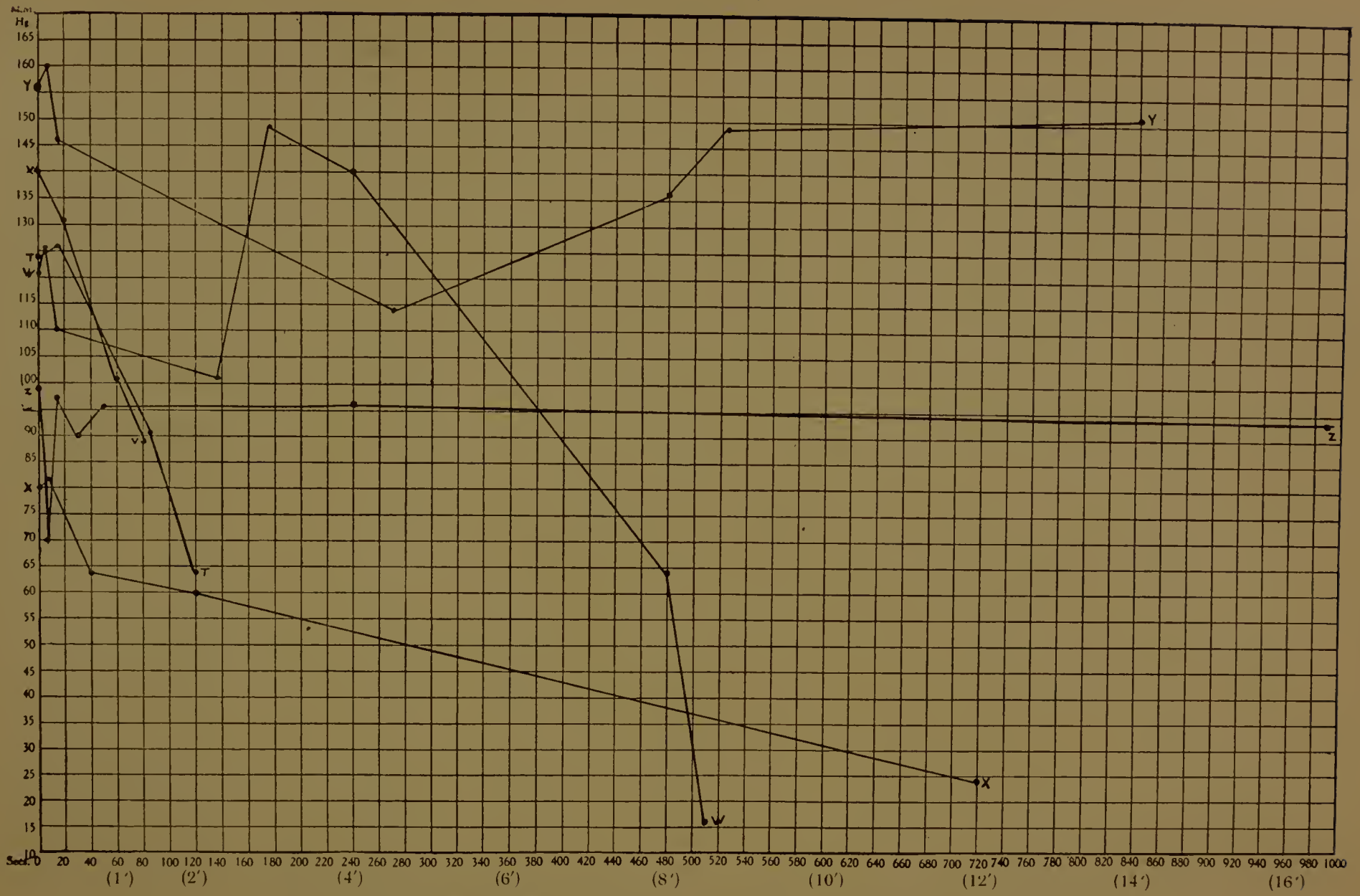
20 °/₀ ethyl chloride in air with vagi cut. (See Record B3 and A5, diagrams 2 and 1, and notes, pages 16 and 14.)

B3. A B.P. of 160 m.m. began to fall immediately, reaching 116 m.m in 108″, the fall being continued to zero. The vagi were electrically stimulated, the left just before and the right about 1′ after cessation of breathing, with an immediate fall each time.

A5. B.P. = 128 m.m. Hg. before inhalation, 1′ after it was 110, and in

DIAGRAM 7.



To show *effect of increasing percentages* of Ethyl Chloride upon Blood Pressure.

Z — 5% Ethyl Chloride—Experiment N.
Y — 7·5% ,, — ,, O.
X — 10% ,, — ,, N.
W — 15% Ethyl Chloride—Experiment O.
V — 20% ,, — ,, A.
T — 33% ,, — ,, D.

2′ 3″ it was down to 95 m.m. After the bag was withdrawn it fell to 72 m.m. whilst the drum was stopped. As when the vagi are intact, there was a steady fall although not so rapid. That the administration can be conducted for a more prolonged period after section of the vagi is doubtless due to the fact that pulmonary ventilation is diminished with lessened intake of the anaesthetic.

The conclusions to be deduced from these experiments are—that 20 °/₀ E.C. vapour in air will lower B.P. rapidly. The more rapid and deep the respiration the more rapid will be the fall.

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33 °/₀ ethyl chloride in air. (See Record D1, diagram 3, and notes, page 19.)

In this experiment 33 °/₀ of E.C. in air was given twice.

When the first administration was begun the B.P. = 123 m.m. Hg. There was a slight initial rise to 127 m.m., but in less than 20″ it was falling—the descent being continuous. In 85″ it had reached 90 m.m., and when the anaesthetic was withdrawn it had dropped to 64 m.m. (The amplitude of the cardiac beats was exaggerated, and in measuring the B.P. the mean was taken.) Artificial respiration ended in recovery of the pressure.

On repetition of the experiment the B.P. = 129 m.m. a slight initial rise in 18″ to 133 m.m. occurred, and was immediately followed by a continuous fall which in 85″ registered 100 m.m., and 10″ later when the anaesthetic was withdrawn it had fallen to 84 m.m. The fall continued until 48″ later when it was down to 39 m.m. Artificial respiration was resorted to and recovery ensued.

The result of these two experiments tend to prove that 33 °/₀ is a dangerous concentration, lowering blood pressure very rapidly, and that restorative measures are effectual even after such a profound depression in the circulation.

To obtain a clear idea of the effects of various percentages of E.C. upon the B.P., I have plotted out a diagram (see diagram 7) to show how increasing the concentration of the vapour increases the effect of the anaesthetic. In plotting out the effect of a 20 °/₀ vapour I chose record A1, because in that experiment the animal had not inhaled any other vapour (except of course the ether which was common to all in the induction of anaesthesia), whereas in E7 the animal had had mixtures of E.C. + O_2 and E.C + CO_2 five times prior to 20 °/₀ E.C. in air.

A study of this diagram will show that 5 % vapour even after an administration of 16′, and that a 7·5 °/₀ vapour after 14′ have barely altered the pressure. It also shows that vapours of 10 °/₀, 15 °/₀, 20 °/₀, and 33 °/₀ lower B.P., and that the more concentrated the vapour the more rapidly is the diminution effected.

The reduction of the B.P. with 20 °/₀ vapour was rather more rapid than with 33 °/₀, which may be accounted for by the fact that with the stronger vapour there was a small preliminary increase in the pressure before the steady fall. A conclusion to be drawn from these results is that it is not the *amount* of E.C. inhaled by the animal which tells, but its *concentration* ; in other words, the higher

the *percentage* of vapour inhaled the more profound the effect produced. In support of this I give the following figures :—

In two of the experiments, B. and O., the amounts of the mixture used were noted.

Experiment B. (with cut vagi).

13 litres of 15 °/₀ vapour were inhaled in 12′.

6 ,, of 20 °/₀ ,, had been inhaled when respiration ceased in 2½′.

13 litres of 15 °/₀ vapour containing **6·5 c.c.** E.C. inhaled in 12′ = 0·541 c.c. per min.

6 ,, of 20 °/₀ ,, ,, **4 c.c.** E.C. ,, ,, 2½′ = 1·6 c.c. ,,

Reference to diagram 2 will show the more pronounced effect of the stronger vapour, although the amount of E.C. inhaled was actually less than with the less concentrated.

Experiment O. (with intact vagi),

18 litres of 7·5 % vapour were inhaled in 14′.

9 ,, 15 % ,, ,, 8½′.

18 litres of 7·5 °/₀ vapour containing **4·5 c.c.** E.C. inhaled in 14′ = 0·321 c c. per min.

9 ,, of 15 °/₀ ,, ,, **4·5 c.c.** E.C. ,, ,, 8½′ = 0·529 c.c. ,,

Reference to diagram 6 will demonstrate the very pronounced effect of the more concentrated vapour, although the total amount of E.C. inhaled was the same in each.

A point worth noting is that in each of these experiments a 15 °/₀ vapour was administered, and that the average amount of E.C. inhaled was almost identical —·541 c.c. per min. in B., and ·529 c.c. per min. in O.

Conclusion. Ethyl Chloride generally produces a short initial rise in B.P., and with vapours of 5 % and 7·5 % the pressure remains high during a prolonged administration. A 10 % vapour can be given for some minutes, but it ultimately seriously reduces the pressure. With 15 % vapours and upwards B.P. quickly falls, the reduction being more rapid the more concentrated the vapour.

THE EFFECT ON B.P. OF MIXING OXYGEN WITH ETHYL CHLORIDE VAPOUR.

The experiments bearing on this are :—

15 °/₀ E.C. + O_2	... ...	Experiment E.
20 °/₀ E.C. + O_2	... ...	,, E.
20 °/₀ E.C. + 50 °/₀ O_2 in air	...	,, A.
20 °/₀ E.C. + 50 °/₀ O_2 in air with vagi cut	... ...	,, A.

For convenience, the notes of the action of various strengths of E.C. in air are briefly repeated when necessary, that a more ready comparison may be made of the effect of mixing oxygen and CO_2 respectively with ethyl chloride.

15 °/₀ ethyl chloride + oxygen. (See Records E1 and 2, diagram 4, and notes, page 20.)

B.P. rose from 156 m.m. to 183 m.m. in 2′, but a clot having formed in the canula a further record was not obtainable until cleared. No control experiment with 15 % E.C. in air was performed, but fortunately the animal used in this experiment was a cat, as was also that in Experiment O. (in which 15 % E.C. in air was given), and (although not strictly accurate) a comparison may be made between diagram 6 and diagram 4.

Reference to page 29 shows that when 15 °/₀ E.C. in air was given the B.P. was = 122 m.m. Hg. A slight rise in 5″ to 126 m.m. was followed by a fall to 110 m.m. after an administration of 15″. A further slight fall occurred, so that after an inhalation of 2¼′ it was = 102 m.m. A rise followed, and in 40″ it was = 148 m.m. when a steady continuous fall occurred. About 5′ later it had dropped to 64 m.m., and 30″ later it was = 16 m.m., and only recovered after a considerable period of artificial respiration.

In experiment E, after clearing the canula of clot, the administration of 15 % E.C. in O_2 was repeated. At the outset the B.P. = 178 m.m. Hg., a slight rise to 186 m.m. was followed by a fall in 42″ to 174 m.m. From this point it continued to rise so that in almost 10′ it was = 200 m.m., and upon withdrawal of the anaesthetic 1′ later it had dropped to 193 m.m.

Conclusion. Oxygen, mixed with 15 °/₀ E.C., prevents the fall of B.P. caused by that concentration in air and has the power of increasing the pressure. The explanation is probable that the O_2 causes the respiration to become more shallow so that although a fairly concentrated vapour of E.C. is given to the animal it inhales a smaller amount of the vapour, and the average intake per min. of E.C. is so diminished that it is equivalent to a weak vapour, the pressure being thus maintained.

20 °/₀ ethyl chloride in oxygen. (See Records E3 and 4, and diagram 4, and notes, page 21.)

On page 22 will be found the result of 20 °/₀ E.C. in air which must be quoted, but as this was administered after inhalations of E.C. + O_2 and E.C. + CO_2 it can hardly be taken as a purely normal effect of 20 °/₀ E.C. in air. It shows, however, that at the beginning of inhalation the B.P. = 148 m.m. In 20″ it rose to 154 m.m. then fell gradually, so that after an inhalation of 2′ it stood at 118 m.m., 2′ later it had risen to 128 m.m.

20 % E.C. in O_2. The B.P. was = 180 m.m., rose to 186 in 6″, and fell so that 89″ later it registered 156 m.m. A rise followed, rapid at first—to 180 m.m. in 22″—then more slowly, so that about 100″ later (that is 220″ from the beginning of inhalation) it was = 184 m.m. From this point it fell and reached 148 m.m. 4′ later, and after an inhalation, covering about 10′, it had still further fallen to 114 m.m.

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20 °/₀ ethyl chloride + 50 °/₀ oxygen in air. (See Records A3, 4, and 4a, and diagram 1, and notes, pages 13 and 14.)

On page 12 the effect of 20 °/₀ E.C. in air upon B.P. was shown to be that from 140 m.m. it rapidly fell in 80″ to 88 m.m.

20 % E.C. + 50 % O_2 in air. Two experiments were performed. In the first the B.P. was, after a very slight rise, lowered from 136 to 112 m.m. in 2′ 27″, with a further fall after withdrawal of the anaesthetic to 106 m.m. in 15″.

The record of the second administration shows that an almost steady fall occurred, taking 6′ 10″ to drop from 134 m.m. to 100 m.m.

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20 % ethyl chloride + 50 % oxygen in air. Vagi cut. (See Record A7, and diagram 1, and notes, page 15.)

On page 14 it has been shown that with 20 % E.C. in air when the inhalation was begun B.P. = 128 m.m. Hg., and a steady fall was caused. During the intervals whilst the drum was stopped it had dipped lower. After an inhalation of 1′ it had fallen to 110, and 63″ later it had reached 95 m.m. A further fall to 72 m.m. occurred whilst the drum was stopped, but how long after is not known. Later (E.C. + CO_2 having been administered in the meantime)

20 % E.C. + 50 % O_2 in air was given.

At the outset B.P. = 138 m.m. Hg. and a gradual fall to 126 m.m. occurred in 120″. 2′ later it had risen to 130 m.m., and this was followed by a fall, so that 65″ later (i.e., after an administration of 5′ 4″) it registered 114 m.m.

Conclusion. On studying these experiments it will be found that O_2 has a markedly beneficial effect with such a concentrated vapour as 20 % E.C. It prolongs the period during which the stronger vapour can be given with safety and delays the fall of B.P. very considerably. I think that the explanation given for the value of O_2 with 15 % holds good here also, but to a smaller extent. The higher percentages of E.C. ultimately reduces the B.P. The period over which 20 % can be administered is more than doubled by giving it with pure O_2, or with 50 % O_2.

THE EFFECT ON B.P. OF MIXING CO_2 WITH ETHYL CHLORIDE VAPOUR.

The experiments bearing upon this are as follows :—

(1) 10 °/₀ E.C. + 2·5 °/₀ CO_2	...	Experiment N.
(2) 15 °/₀ E.C. + 10 °/₀ CO_2	...	,, E.
(3) 20 °/₀ E.C. + 10 °/₀ CO_2	...	,, A. & E.
(4) 20 °/₀ E.C. + 10 °/₀ CO_2 (with vagi cut)	... ...	,, A.
(5) 33 °/₀ E.C. + 5 °/₀ CO_2	...	,, D.

10 % ethyl chloride + 2·5 % CO_2 in air. (See Record N4, diagram 5, and notes, page 26.)

On reference to page 26 it will be seen that 10 % E.C. in air was administered twice to this animal, and as in the second one the initial B.P. was almost identical with that when E.C. + CO_2 mixture was given, I shall take it for comparison.

At the outset B.P. = 80 m.m. After a slight rise it fell in 40″ to 64 m.m., and then a steady continuous fall to 24 m.m. in 12′.

With *10 % E.C. + 2·5 % CO_2 in air* the B.P., which was = 76 m.m. at the beginning of inhalation after a slight initial rise to 78 m.m., immediately began to fall, and in 2½′ reached 48 m.m., and 2′ later it was down to 32 m.m., the fall still continued, so that 5½′ later it had dropped to 20 m.m.

Artificial respiration was necessary after both administrations to restore the animal.

It may be concluded that carbonic acid in this strength increases the potency of ethyl chloride vapour.

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15 % ethyl chloride + 10 % CO_2 in air. (See Record E5, diagram 4, and notes, page 21.)

B.P. was = 152 m.m. at the outset, and a rise to 162 m.m. occurred in 10″. This was maintained for about ½′, and was followed by a gradual fall within 2′ to 140 m.m.. A continuous fall to 110 m.m. during the next 9′ was recorded.

In experiment O a record during the inhalation of 15 % E.C. in air was obtained, from which it was shown (see page 27) that with a vapour of that concentration after 3′, during which a rise of B.P. occurred, a rapid fall took place, and with an inhalation of 8½′ required artificial respiration for its recovery.

Comparison of these two experiments (though not strictly accurate being in different animals) would lead one to conclude that CO_2 added to 15 % of E.C. causes an earlier and more gradual fall than with E.C. in air alone.

20 % ethyl chloride + 10 % CO_2 in air. (See Records A2 and E6, diagrams 1 and 4, and notes, pages 13 and 21.)

Experiment A. On page 12 is shown, the effect on B.P. of 20 % E.C. in air as a constant fall from 140 m.m. to 132 m.m. in 20″, to 102 m.m. in 60″, and to 88 m.m. in 80″.

(A2) *20 % E.C. + 10 % CO_2 in air.* At the outset the B.P. = 146 m.m., a rise in 22″ to 152 m.m. was followed by a constant fall to 124 m.m. in 79″, and a further fall to 110 m.m. 20″ later.

Here we see that a preliminary rise occurred when CO_2 was present, which was absent without it. The subsequent fall was not quite so profound with the mixture as with E.C. alone in air.

Experiment E. On page 22 are notes of the action of E.C. 20 % after inhalations of E.C. in air, E.C. + O_2, and E.C. + CO_2, and although probably not a true record of E.C. 20 %, because of the previous O_2 and CO_2 it must be used to compare this effect of the addition of 10 % CO_2 to 20 % E.C. In it we see that B.P. rose from 148 to 154 m.m. in 20″, then a gradual fall to 118 m.m. in 2′ followed by a rise to 128 m.m. during a further period of 2′.

(E6) *20 % E.C. + 10 % CO_2 in air.* Administration of this mixture caused a preliminary rise from 168 to 178 m.m. in 25″, a rapid fall to 148 m.m. followed in 15″, when an upward phase to 164 m.m. in 100″ began. From this height it steadily fell, so that when the anaesthetic was withdrawn after an inhalation of 5′ it had dropped to 98 m.m.

Conclusion.

In this experiment we see that although the preliminary rise was somewhat greater and slightly more prolonged with the combination of E.C. and CO_2 the subsequent fall was sharper and the following rise less sustained, being succeeded by another great fall, pointing to a conclusion that 10 % CO_2 increases the power of a 20 % vapour of E.C. to reduce B.P.

---

20 % ethyl chloride + 10 % CO_2 given with the vagi cut. (See Record A6, diagram 1, and notes, page 15.)

Reference to page 14 shows that with 20 % E.C. in air there was a persistent fall in B.P. from 128 m.m. to 110 m.m. in 60″, and a further fall to 95 m.m. in the next 63″. A fall to 72 m.m. occurred in an unknown time whilst the drum was stopped.

20 % E.C. + 10 % CO_2.

An administration of vapour of the same strength of E.C. with the addition of 10 % CO_2 was conducted after an interval of a few minutes, by which time the B.P. was = 120 m.m. Hg. ; a rise to 130 m.m. in 15″ occurred, followed by a fall to 100 m.m. 45″ later. This level was barely altered when the anaesthetic was

withdrawn in 4½′, but it fell, during the interval in which the drum was stopped, to 30 m.m. Artificial respiration was conducted, and recovery occurred. This mixture, when given to the same animal before section of the vagi, caused an initial rise of B.P.

A conclusion which may be arrived at from this experiment is that CO_2 caused a smarter fall in B.P. The ultimate serious fall possibly was due to the combined toxic effects of the CO_2 and E.C.

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33 % ethyl chloride + 5 % CO_2. (See Record D3, diagram 3, and notes, page 20.)

Records of two administrations of 33 % E.C. in air having been obtained, the second is chosen for comparison, being the one immediately preceding the inhalation of the mixture of E.C. and CO_2.

On page 19 the notes of the effect of the administration of 33 % E.C. in air upon B.P. show a slight rise from 129 to 133 m.m., followed by a fall to 100 in 85″. The rapid fall continued, even after the anaesthetic was withdrawn, to 39 m.m. in less than 2½′. Artificial respiration was performed.

33 % E.C. + 5 % CO_2 in air.

Repetition of the experiment with the addition of 5 % CO_2 was performed. Here a marked rapid initial rise occurred from 126 m.m. to 146 m.m. in 5″, and this was followed by a fall to 95 m.m. in 96″ from the time the bag was attached. Artificial respiration was carried out after this experiment also.

The conclusion one can arrive at from this experiment also is—that after briefly increasing B.P., CO_2 adds to the rapid lowering of B.P. by this high percentage of E.C.

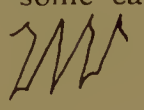
Conclusions. The effect upon B.P. of the addition of 2·5 % or more of CO_2 to E.C. vapour is that it produces or increases a transitory initial rise, and for a time maintains B.P. by its cardiac stimulant action but afterwards causes a more rapid fall.

General Conclusions as to the effect of Ethyl Chloride upon Blood Pressure.

Generally an initial rise occurs with various concentrations of vapour. With weak vapours an excellent pressure is maintained throughout administrations covering several minutes, but higher percentages cause a fall which is more rapid and profound the higher the concentration. Embley[3], Webster[4], and Cole[5] each found that an initial rise and subsequent fall occurred, so that my results agree with theirs in this respect. My experiments also point to the markedly beneficial effect of combining oxygen with ethyl chloride in maintaining blood pressure during a much longer administration than is possible with the same strength of ethyl chloride only. CO_2 by its cardiac stimulant action sometimes increases or maintains for a time B.P., but, except in very small proportions, it ultimately causes a more rapid fall from the combined toxic effects of the two vapours.

RELATIONSHIP OF THE HEART TO BLOOD PRESSURE.

That the state of B.P. depends upon that of the heart is, I think, proven by the following facts gathered from my records.

In Record A1 the B.P. is seen to have "dipped" 5 times, once before ethyl chloride was administered, twice whilst it was being inhaled, and twice after its withdrawal. In every instance some cardiac arrhythmia is shown, the tracing having the following character  , being devoid of notches.

In Record A2 "dips" of B.P. occur more frequently, and here again the heart record shows synchronous unnotched tracings.

Nothing in the respiration record is seen during these temporary falls of B.P., which occurred even during respiratory paralysis. It is also seen that B.P. remains good during respiratory paralysis so long as the heart beats are good.

Did B.P. depend upon respiration a fall to zero should occur when paralysis of that function appears, which does not happen.

Returning to experiment C. (see Records C1 to 7 and notes, page 17), it has been proven that the blood vessels contract. Synchronous with the fall in K.V. the B.P. falls, therefore the lowering of B.P. is not due to dilatation of the blood vessels, but to cardiac weakness. That it is not a central, but a cardiac effect is demonstrated by the fact that the results were the same after section of the vagi as when they were intact.

The following figures show the dependence of B.P. upon the heart :—

	Heart rate fell	B.P. fell
With vagi intact—		
20 % E.C. in 80″	from 140 to 120 per min.	from 140 to 88 m.m.
20 % E.C. + 10 % CO_2 in 95″	,, 140 to 116 ,,	,, 146 to 110 ,,
20 % E.C. + 50 % O_2 in 6′ 10″	,, 180 to 93 ,,	,, 134 to 100 ,,
25 % E.C. in 5″	,, 240 to 216 ,,	,, 102 to 87 ,,
33 % E.C. in 85″	,, 86 to 66 ,,	,, 129 to 100 ,,
With one vagus cut—		
12·5 % E.C. in 150″ ...	,, 192 to 174 ,,	,, 134 to 94 ,,
25 % E.C. in 103″ ...	,, 229 to 213 ,,	,, 136 to 100 ,,
35 % E.C. in 19″ ...	,, 213 to 198 ,,	,, 130 to 78 ,,
With both vagi cut—		
20 % E.C. in 1¾′ ...	,, 216 to 142 ,,	,, 130 to 95 ,,
20 % E.C. + 10 % CO_2 in 4′	,, 204 to 162 ,,	,, 120 to 100 ,,
20 % E.C. + 50 % O_2 in 4′	,, 204 to 168 ,,	,, 140 to 134 ,,
25 % E.C. in 35″ ...	,, 228 to 144 ,,	,, 116 to 82 ,,

The fact that analogous results occurred with the vagi intact, one vagus cut,

and both vagi cut, points conclusively to this not being central but due entirely to the effect of ethyl chloride upon the heart muscle. A further proof of this is found in the following table, in which the amplitude in millimetres of the heart tracing is given for ethyl chloride with oxygen and CO_2 respectively, whilst the vagi were intact and after they were cut.

Amplitude of heart tracing.

	Vagi intact.	Vagi cut.
20 % E.C. + 10 % CO_2 ...	unaltered ...	decreased from 5 to 1 m.m.
20 % E.C. + 50 % O_2 ...	unaltered ...	,, 7 to 3 m.m.

It has already been shown that the heart rate was reduced in both instances, the amplitude, however, was unaltered whilst the vagi were intact from the central action of CO_2 and oxygen respectively On section of the vagi this central action was eliminated, and the effect of ethyl chloride upon the heart muscle was to reduce the rate and amplitude of the cardiac beat as well as to lower the B.P.

The foregoing facts, from different points of view, prove that the condition of *the B.P. is directly dependent upon the condition of the heart.*

EFFECT OF ETHYL CHLORIDE UPON RESPIRATION.

This was carried out to show the effect of various strengths of ethyl chloride

(1.) In air ;
(2.) With oxygen or with oxygen and air ;
(3.) With CO_2 and air.

THE EFFECT OF ETHYL CHLORIDE IN AIR UPON RESPIRATION.

The experiments dealing with this are :—

With intact vagi—

5 %	...	Experiment N.
7·5 %	...	,, O.
10 %	...	,, N.
15 %	...	,, O.
20 %	...	Experiments A and E.
33 %	...	Experiment D.

With cut vagi—

15 %	...	,, B.
20 %	...	Experiments B and A.

5 % ethyl chloride in air. (See Record N1, and notes, page 25.)

Normally the respirations numbered 22 per min. and were deep.

The stoppage and irregularity, which is seen to have occurred at the commencement of inhalation, was due to the forcible expression of the anaesthetic vapour from the overdistended bag as it was applied to the inspiration tube. On normal breathing occurring, and after 11 respirations, they became much more shallow—$\frac{1}{3}$ or $\frac{1}{4}$ of the normal. The effect passed off in 1′, and was followed by much deeper and slower respirations, and towards the end of the inhalation, which lasted $16\frac{1}{2}$′, they were almost as fast but deeper than normal. This stimulation continued and even increased for at least 3′ after the anaesthetic was withdrawn.

This experiment proves that a 5 % vapour can be given for many minutes ($16\frac{1}{2}$) and that its action is markedly stimulative to respiration, and that the stimulation persists after inhalation of the vapour ceases.

7·5 % ethyl chloride in air. (See Record O1 and notes, page 27.)

In this animal the respiration was very rapid, the normal being 230 per min., but the amplitude was good. At the beginning of inhalation it was somewhat

slower and much deeper, becoming still slower (84 per min.) with deep inspirations. In 1′ the normal rate and amplitude were regained, lasting 2½′, this was followed by the slower type of breathing again, the depth increasing about 50 %. This was succeeded by respiration approaching normal, and from this point till the end of the administration (a period of about 7′) the increase in depth to 30 % above normal, and the decrease in rapidity to 78 per min. were gradual. The administration lasted for 14′, and was stopped because of the exhaustion of the bag.

It may be concluded from this that a vapour of 7·5 % E.C. can be given for many minutes without seriously affecting respiration, and that it stimulates the depth of breathing

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10 % ethyl chloride in air. (See Records N2 and 3 and notes, page 25.)

In the first of these administrations the respirations just prior to inhalation were 21 per min. and deep. The first effect was 6 shallow respirations which were about ⅕ of the amplitude of the normal. These were followed by deeper (½ normal) and more rapid breathing (38 per min.). In 1′, however, they quickly increased in depth and slowed down to normal. After an inhalation of 9′ the breathing was still as deep as the normal, but had become faster (38 per min.), the rapidity increasing so that 3′ later it had a rate of 46 per min. without any reduction in amplitude. The B.P. having fallen, the administration was stopped, and the respiration ½′ later showed signs of failure, complete paralysis quickly supervening, necessitating artificial respiration.

On recovery a second administration of 10 % E.C. was conducted.

At the outset respirations numbered 20 per min., and 2′ later were 18 per min., the depth having diminished to about ⅓ of the normal. 9′ later respiratory failure had set in, and complete paralysis developed quickly. Recovery occurred with artificial respiration.

The deductions to be drawn from these two experiments are that 10 % E.C. has a stimulative action upon respiration, but when given in this strength for several minutes (12) causes rapid respiratory paralysis. If, after recovery from respiratory paralysis, E.C. of the same concentration is again given, the early stimulant effect is not produced.

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15 % ethyl chloride in air. (See Record O2 and notes, page 27.)

This at first caused the animal to breathe in a shallow manner with the chest in a position of expiration, during which a single deep breath was taken, and gradually did the chest resume its normal condition during respiration, which by degrees became much slower (from 230 to 54 per min.); marked arrhythmia set in after an inhalation of about 2½′. The administration lasted 8½′. Paralysis occurred later, and energetic artificial respiration was necessary for recovery. It may be concluded that 15 % E.C. vapour in air soon causes weakening of the respiratory apparatus followed by paralysis.

20 % ethyl chloride in air. (See Records A1 and E7 and notes, pages 12 and 22.)

A1—Just after inhalation was begun respirations were equal to 60 per min., and 20″ later hyperpnœa developed, breathing becoming deeper and faster, both depth and rapidity increasing so quickly that with an inhalation of less than 1′ the rate increased to 148 per min., and the depth more than doubled. With the withdrawal of the anaesthetic in 60″ the respiration rapidly diminished in depth and frequency, and 15″ later breathing ceased.

E7—When the administration was begun the rate of respiration was 15 per min., and after 4 shallower and slower breaths the rate increased. At the end of 2′ the respirations numbered 18 per min., and when the inhalation was discontinued at the end of 4′ they were 48 per min. and very shallow. This latter experiment was performed in an animal which had already been subjected to 3 experiments with E.C. + O_2 and 2 with E.C. + CO_2. This is not nearly so reliable as to the action of 20 % E.C. as experiment A1.

Conclusion. The experiment E7 shows the gradual paralysing effect of this strength of vapour.

Experiment A1 shows a marked initial stimulating action and rapidity of failure of respiration by 20 % ethyl chloride.

This very rapid paralysis of respiration is the result of two causes. (1) The high percentage of E.C. and (2) the fact that hyperpnœa causes increased intake of that vapour. A glance at the record shows how the weakening increased, and ultimate failure resulted after the withdrawal of the anaesthetic, this being the result of the large amount of E.C. absorbed during inhalation for one minute only.

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33 % ethyl chloride in air. (See Record D1 and notes, page 19.)

The respiration just after inhalation was begun was very irregular, but this condition passed off, the rate of breathing being 57 per min. A stimulant action followed, the respirations becoming faster (78 per min.) and deeper (about 3 times as great). In 1′ the breathing began to fail, and 38″ later was completely paralysed. The lever gradually rose during this increasing paralysis on account of the chest having by degrees approached a deep expiratory position. Four exceedingly shallow attempts to breathe were made after respiration stopped.

This experiment was repeated when recovery by artificial respiration had occurred.

With the re-introduction of the vapour into the lungs the respiration was slightly irregular and slow (36 per min.), but in a few seconds became faster and regular. Hyperpnœa set in in 40″, the respiration increasing in frequency to 160 per min. and to double the depth. Rapid respiratory paralysis set in, absolute cessation of breathing occurring after an inhalation of 85″. The profound expiratory position of the chest during the paralysis (which had gradually increased during the weakening) was seen here also as in the previous experiment. In this

experiment an attempt to restore the animal was made by an intravenous injection of Ringer's Solution saturated with CO_2, but it had not the slightest effect. The usual method of artificial respiration (by blowing through the inspiratory tube) was followed by recovery which, however, was in this case very gradual though complete.

The conclusions to be deduced from these two experiments are that 33 % E.C. in air initially stimulates respiration, and that it causes very rapid respiratory paralysis ; also that the respiratory apparatus during the failure assumed more and more the position of expiration.

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15 % ethyl chloride in air with vagi cut. (See Record B2, and notes, page 16.)

In Record B1 we see the normal respiratory tracing, and that obtained after section of the vagi. The normal rate of breathing was 21 per min., but when the vagi were cut it became slower (9 per min.) and irregular whilst the depth was increased to less than double. Just prior to the administration the respiration had quickened to 12 per min., whilst the depth had again diminished, yet not so low as normal. On inhalation of the anaesthetic (15 % E.C. in air), the first effect was slowing and deepening but soon gaining in rapidity. After a further inhalation of 2′, the respirations were 21 per min. and about the normal depth. The shallow character and rapidity increased more and more until, on the verge of paralysis, the inhalation was stopped.

13 litres of mixture were inhaled in 12′.

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20 % ethyl chloride in air with vagi cut. (See Records B3 and A5, and notes, pages 16 and 14.)

B3.—Breathing rate was 13 per min., and with the inhalation of the anaesthetic it was slower and deeper, soon becoming more and more shallow and rapid, until paralysed $2\frac{1}{2}'$ after attachment of the bag. Death of the animal followed.

Another experiment with this strength of vapour was performed (see Record A5.)

Respirations, after section of the vagi, were slower than normal (32 per min), and on administration for 1′ of 20 % E.C. in air the rate was 66 per min. and only slightly shallower. 55″ later, and until the bag was removed after an attachment for 123″, paralysis increased, and it was difficult to say whether the waves in the stethogram were respiratory or cardiac beats, but were probably the latter, being equal in number to those in the cardiogram.

On studying these records it is found that, after section of the vagi, E.C. can be administered for a longer period than when intact.

In experiment A the duration of administration of 20 % vapour was doubled after section, and the hyperpnœa produced prior to section was not present in the later experiment. This longer administration may have been due to two causes.

Professor Milroy, in his experiments on "The Regulation of Breathing" (communicated to a meeting of the Ulster Medical Society), found that, on section of the vagi, the breathing was slowed and that the depth was not proportionately increased, therefore pulmonary ventilation is diminished. Now, that being so, the amount of anaesthetic absorbed by the blood would be less. Secondly, the absence of hyperpnœa does away with the rapid intake and absorption of anaesthetic, the result being that the amount absorbed in a given time (say per min.) is less when the vagi are cut than when intact, and paralysis is delayed.

It will be noticed that in experiment A5, on giving the 20% vapour, the respiration was stimulated as regards rapidity, but the depth was slightly diminished.

In experiment B the reverse occurred, both when 15% and 20% vapours were given, the respiration was slowed and the depth increased slightly.

The period during which it was possible to give the 15% E.C. was certainly longer than that in experiment O, with vagi intact, when the same concentration was administered, which possibly may have been due to diminution of pulmonary ventilation (as already mentioned) causing a lesser absorption of anaesthetic, but one must not overlook the fact that it may be the result of "the personal element"—the two animals possibly not reacting alike to the same strength of vapour. This may be perhaps a suitable place to mention a possible source of error in forming conclusions from examination of various records. If the records being compared are obtained from *different* animals this "personal element" (with which anaesthetists are familiar clinically) cannot be estimated. If, on the other hand, a series of experiments are performed on the same animal during an afternoon it is equally impossible to estimate the effect of fixation of a certain amount of anaesthetic in the first or early experiments to the detriment of results in later ones. Here again anaesthetists are familiar with the fact that the longer an anaesthetic is administered the less is required—what may be considered a sort of immunisation—and although E.C. is so very volatile I have known of this anaesthetic being voided in the breath of patients for hours.

The vagi contain fibres which carry from the lung afferent impulses to the respiratory centre, and when these nerves were divided in experiment A5 there was not the marked stimulation which had been obtained in experiment A1 in which the vagi were intact. E.C. therefore stimulates the pulmonary fibres of the vagus which convey afferent impulses to the respiratory centre.

In A5 and in experiment B, in both of which the vagi were cut, there was but slight respiratory stimulation, which was doubtless the effect of E.C. in the blood supplied to the respiratory centre.

The stimulation of respiration is therefore caused (1) chiefly by the action of E.C. in stimulating the fibres of the vagus in the pulmonary tissue, and (2) in a small degree by the E.C. in the blood affecting the centre in the medulla.

Since forming these conclusions, by a study of my records, I have read two articles by L. Camus and M. Nicloux[6]. In one of these they say that two distinct phases are to be seen in the acceleration of breathing, corresponding to two different actions of the ethyl chloride. The first, which appears about the second minute, is relative to a peripheral excitation; and the second, which is seen about the 6th or 8th minute, is dependent upon central excitation. Section of the vagi (they continue) abolishes the primary polypnœa, but the secondary polypnœa appears about the 8th minute.

My records show these effects appearing earlier than the times mentioned by Camus and Nicloux.

General conclusions with regard to the action upon respiration of ethyl chloride in air.

Ethyl chloride possesses an initial stimulant action upon respiration which is sometimes great and at other times slight. The weaker the vapour inhaled the more prolonged is the stimulant action and conversely, the more concentrated the vapour the more rapidly is the stimulant effect followed by respiratory failure and paralysis. Especially is this so when hyperpnœa causes a rapid absorption of a dangerous strength of vapour. Respiration ceases before the heart. These conclusions agree with those of Cole[5], Embley[3], and Webster[4].

Stimulation is the result of a local as well as of a central action of the drug, the direct action upon the respiratory centre being much less important than the secondary action conveyed to it through the afferent fibres of the vagus.

Paralysis sometimes occurs with the chest in the position of deep expiration. This agrees with the finding of Cole[5] that "with large doses the diaphragm is finally brought to a standstill, remaining in a state of strong tonic contraction until death ensues, the heart still beating strongly."

Recovery from respiratory paralysis was sometimes spontaneous, and even in cases where paralysis was more persistent artificial respiration was markedly successful in restoration of the animals.

THE EFFECT UPON RESPIRATION OF THE ADDITION OF OXYGEN TO ETHYL CHLORIDE VAPOUR.

The experiments dealing with this are :—

15 % E.C. + O_2	Experiment E.
20 % E.C. + O_2	Experiments A & E.
20 % E.C. + O_2 (with vagi cut)	Experiment A.

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15 % ethyl chloride in oxygen. (See Records E1 and E2, and notes, page 20.)

E1—The administration in this experiment was a short one of 3′, and was stopped because of clotting in the B.P. canula. The Record (E1) shows that the respirations, which were 21 per min. at the beginning, slowed down to 18 per min., and were shallower.

E2—After clearing the canula the experiment was repeated, and at the outset the respiration rate was 22 per min. 2′ later it was slower (13 per min.) and shallower, a condition of *almost complete* apnœa being shown (this is seen in the record taken after an interval of 5′ during which the bag was kept on). Then follow very rapid and shallow respirations which were increasing in depth towards the end of an administration lasting 11 mins. This shallow rapid breathing after apnœa is probably due to the CO_2 generated and retained within the organism exerting a stimulating action upon the respiratory centre.

Conclusion. This experiment proves that the presence of O_2 mixed with 15 % E.C. vastly increases its safety, it having been seen (compare Record O_2) that that percentage of E.C. in air rapidly paralyses respiration with fall of B.P. demanding artificial respiration.

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20 % ethyl chloride + oxygen. (See Records E3 and 4, A3, 4 and 4a, and notes, pages 21, 13 and 14.)

E3 and 4—Just prior to inhalation the respirations were 14 per min., and 30″ later were slower (12 per min.) and shallower. After 2′ they increased in rapidity to 22, and still later to 44 per min., becoming more and more shallow. After a period of this very quick and shallow breathing the respiration approached in type that which was present about 1′ after inhalation was begun, viz., shallow and slow. This administration lasted for over 10′.

A3, 4 and 4a. In these two experiments the proportion of O_2 in the mixture was 50 %.

The rate of breathing, just before administration was begun, was 90 per min. With the application of the bag a short period of apnœa occurred, followed by shallow respirations which gradually increased in depth and frequency (165 per min.) and somewhat deeper than those prior to administration of the anaesthetic. Apnœic phases supervened in 1′ 29″, becoming more and more frequent till the anaesthetic was withdrawn in 2′ 27″, the cardiograph pointer having loosened.

The experiment was repeated, and, although more than a quarter of an hour had elapsed since the previous inhalation had ceased, the effect of the O_2 had persisted in that the respirations were very much slower, viz., 57 per min. In less than 1′, after attaching the bag of vapour, periods of diminished frequency and force of respiration set in, and periods of apnœa alternated with periods during which the breathing was quicker. The administration lasted 6′ 10″, towards the end of which irregularity became very pronounced.

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20 % ethyl chloride + 50 % oxygen in air (with cut vagi.) (See Record A7, and notes, page 15.)

Respiration, which had been at the rate of 12 per min. before inhalation, showed some irregularity on attachment of the bag, which passed off in a few seconds. During the remainder of the inhalation phases of more rapid (60 per min.) and deep, alternated with slow (24 per min.) and shallow breathing, but the type of respiration was better than when this mixture was given with the vagi intact, the irregularity seen then was not present when the vagi were cut. The inhalation lasted 5′ 4″.

From these experiments it may be concluded that such a potent percentage of E.C. as 20 % is rendered comparatively innocent by mixing oxygen with it.

General conclusions as regards mixtures of E.C. and O_2 upon respiration.

Oxygen has a beneficial effect in that it robs the higher percentages of E.C. vapour of their paralysing action upon respiration. Such strengths of E.C. vapour as 15 % and 20 %, which soon cause respiratory paralysis, can, when O_2 is added, be given for much more extended periods without that effect. The reason for this undoubtedly is that the inhalation of O_2 diminishes the depth and frequency of breathing with the result that, although a higher percentage of E.C. is actually presented to the animal, the amount actually absorbed in a given time is greatly diminished ; or, in other words, the average amount per min. inhaled by the animal is diminished, bearing out the conclusion arrived at in considering the effect of E C. on B.P., that it is not the actual amount but the proportion per min. inhaled which tells.

Artificial respiration has not been necessary in any of the experiments in which oxygen was mixed with ethyl chloride, although it was demanded after inhalations of the drug, varying in strength from 10 to 33 %, in air or with CO_2 in air.

THE EFFECT UPON RESPIRATION OF ADDING CO_2 TO ETHYL CHLORIDE.

The experiments bearing upon this are :—

10 % E.C. + CO_2	...	Experiment N.
15 % E.C. + CO_2	...	,, E.
20 % E.C. + CO_2	...	Experiments A and E.
33 % E.C. + CO_2	...	Experiment D.
With vagi cut—		
20 % E.C. + CO_2	...	,, A.

---

10 % ethyl chloride + 2·5 % CO_2 in air. (See Record N4 and notes, page 26.)

The Respirations which were deep with a rate of 16 per min. before the mixture was inhaled became a little shallower when the administration was started. This was followed after a few breaths by deeper breathing which, however, soon became gradually more and more shallow (about ½ the depth obtaining before inhalation began). After administration for 7′ it had quickened to 22 per min. and become more shallow, 2′ later paralysis supervened. The paralysis occurred with the chest in the position of expiration, but not (as occurred in another experiment—D) exaggerated expiration. Artificial respiration was necessary for recovery.

Comparing this with the previous experiment in which E.C. 10 % in air was given we see that temporary slight respiratory stimulation occurred after a few breaths, and that respiratory paralysis came on more quickly. CO_2, in the proportion of 2·5 %, given continuously with 10 % E.C., hastens respiratory paralysis.

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15 % ethyl chloride + 10 % CO_2 in air. (See Record E5 and notes, page 21.)

Breathing, which had a rate of 14 per min., had increased 2 per min., after an inhalation of 2′. At the end of 4′ there was almost complete paralysis, but gradually shallow breathing reappeared with a rapidity of 60 per min. after the bag had been attached for 6′; the respirations numbered 66 per min. when administration was suspended—at the end of 11′. The tambour was inflated during the latter part of the experiment, so that a comparison of the depth of breathing about 5′ before the end of the experiment is impossible.

(This animal had already been submitted to 3 inhalations of E.C. + O_2 and the effect produced by the latter undoubtedly prevented to some, perhaps a large,

degree the normal action of E.C. and CO_2 as would be seen in a perfectly normal animal, Professor Milroy having shewn in his experiments on "The Regulation of Breathing" (already referred to) that a preliminary inhalation of oxygen will prevent increased respiration, and the formation of acid products within the organism due to the using up of the oxygen, and which act like CO_2).

20% ethyl chloride + 10% CO_2 in air. (See Records E6 and A2, and notes, pages 22 and 13.)

This was the fifth experiment on this animal :—

E6—Two minutes after an inhalation of 45″ which was stopped because of the manometer being accidentally turned off, the bag containing 20% E.C. + 10% CO_2 was reapplied to the inspiratory tube.

Respiration had a rate of 18 per min., becoming slower (15 per min.), then more rapid and less deep. The rapidity gradually increased and the depth diminished, and after 140″ breathing was at the rate of 54 per min., and at the termination of an administration of 5′ the rate was 64 per min., and the depth just half of the normal.

A2—This experiment can be accepted in preference to the foregoing as showing the effect of CO_2 mixed with 20%, being the 2nd experiment on this animal, the earlier one having been the administration of 20% E.C. in air. As the anaesthetic was applied to the inspiratory valve the respirations were 96 per min. The inspirations immediately assumed a shallow character, but in a few seconds they regained the normal, quickly becoming faster and deeper. Marked hyperpnœa set in in 30″, the rate being 156 per min. and the depth double the normal. After an inhalation of 65″ rapid paralysis occurred, the bag not being removed till 14″ later.

Comparing this result with that produced by E.C. 20% in air (see page 12) we find that hyperpnœa was 10″ later in appearing due, no doubt, to the shallow respiration at the beginning of inhalation of the E.C. + CO_2 mixture. Complete respiratory paralysis appeared in 74″ from the time that inhalation of E.C. in air was begun, whilst it set in in 65″ with E.C. + CO_2.

From the onset of hyperpnœa in the former the paralysis occurred in 50″, whilst in the latter there passed only 35″ between the onset of hyperpnœa and complete paralysis.

The conclusion is that CO_2 stimulates respiration, and with E.C. forms a more potent mixture than E.C. and air.

Vagi Cut.

20% ethyl chloride + 10% CO_2 in air. (See Record A6 and notes, page 15.)

The hyperpnœa produced by the same mixture with the vagi intact was entirely absent. Respiration was somewhat irregular for 8″ but passed off. The rate was diminished from 30 to 24 per min., and the depth increased a little. In 1′ the breathing was very irregular, shallow, and fast, and 20″ later some

attempts at deeper respiration were made. Paralysis, necessitating artificial respiration, followed, and the animal recovered. Bag was attached for 4½'.

The result of this experiment is analogous to those with E.C. in air with cut vagi, inasmuch as we find that hyperpnœa does not occur as it did when E.C. + CO_2 mixture was given with intact vagi, because the afferent impulses produced upon the vagi in the pulmonary tissue could not be transmitted to the respiratory centre. Yet a slight central stimulation is shown in the small increase in the depth of breathing. On account of the diminished pulmonary ventilation paralysis did not set in so quickly as when the vagi were intact.

---

33 % ethyl chloride + 5 % CO_2. (See Record D3 and notes, page 20.)

On beginning the administration the respiratory rate was 60 per min., and immediately it became deeper and quicker until in 68″ the rate was 87 per min. with double the amplitude. Paralysis quickly supervened, and the anaesthetic was withdrawn 5″ later. Complete cessation of breathing occurred with the chest in the expiratory position. Recovery gradually occurred with artificial respiration.

Conclusion. On comparing this with the effect of 33 % E.C. in air it is found that the respiratory paralysis occurs earlier with the addition of CO_2.

During this experiment (D) the respiratory stimulant action of CO_2 when injected intravenously as a saturated solution in "Ringer" was tested during respiratory paralysis, but it failed completely. Its stimulant effect, however, was witnessed at once on passing the gas through a tube placed in the trachea, the breathing quickly becoming exaggerated. The effect of CO_2 upon respiration, which was not paralysed is seen in records D2 and D3, which show that a very few breaths of the gas produce a decidedly stimulating effect. All the experiments go to prove that CO_2 acts chiefly, if not entirely, upon the terminals of the afferent fibres of the vagus, conveying an impression to the respiratory centre, and supports the conclusion of Wood and Cerna [10] that CO_2 acts by stimulating the vagus.

That very small percentages of CO_2 with ethyl chloride have a beneficial action, has been proven clinically by Hewitt [11]. He employed various methods of administering the anaesthetic—no re-breathing, partial re-breathing, and re-breathing of ethyl chloride and air—and the last mentioned method gave better results. It was subsequently found that this answered less satisfactorily than methods in which the patient's own expired air, as opposed to fresh air, was used to partially fill the inhaler prior to the gradual introduction of the ethyl chloride.

General conclusions with regard to the action upon respiration of ethyl chloride + CO_2 in air.

Small amounts of CO_2 stimulate respiration by its stimulant action upon the vagus, but the proportions used with ethyl chloride in these experiments show a transient or no such effect, but rather increases the potency of the anaesthetic by causing earlier respiratory paralysis.

When required to resuscitate animals during these experiments the method adopted was to apply the lips to the inspiratory valve and to inflate the lungs, using pressure to the thorax for expiration if necessary. This proved eminently satisfactory, and is shown especially in experiment O2 in which the B.P. tracing demonstrates absence of heart beats. As paralysis may occur with the chest in the position of expiration inflation may be the first step towards success. The presence of CO_2 in the air blown into lungs probably also has a very beneficial effect in stimulating the afferent fibres of the vagus. The value of this method clinically is obvious.

THE EFFECT UPON THE HEART OF ETHYL CHLORIDE BY INHALATION.

The methods used in this investigation are detailed upon pages 9 and 10, and the experiments dealing with it are as follows : —

Experiment A. To show the action of—
20 % E.C. in air,
20 % E.C. + 10 % CO_2 in air, and
20 % E.C. + 50 % oxygen in air,
with vagi intact and vagi cut.

Experiment F. To show the effect of—
15 % E.C. in air, and
20 % E.C. in air,
with vagi intact ; and of
15 % E.C. in air,
15 % E.C. + 46·6 % oxygen in air,
15 % E.C. in oxygen and
15 % E.C. + 6·6 % CO_2 in air,
with vagi cut.

Experiment L. To show the effect of—
25 % E.C. in air, with vagi intact and vagi cut.

Experiment M. To show the effect of—
6·6 % E.C. in air, with vagi intact.

Experiments A and L were performed by method No. 1., i.e., by a needle passed through the thoracic wall into the cardiac muscle.

Experiment F was carried out by method No. 2—a plethysmographic record.

Experiment M was performed by method No. 3—two double tambours.

As the effects upon the heart are investigated by different methods during inhalation, and also by perfusion of the isolated heart, the experiments will be taken seriatim and the conclusions drawn, as probably giving better results than by classifying the various percentages of vapours and mixtures, as was adopted in studying their effects upon B.P. and respiration.

Experiment A. 20 % ethyl chloride in air (vagi intact.) (See Record A1, and notes, page 12.) Needle in the heart.

The heart beats at the beginning of inhalation were 140 per min., an occasional increased systole occurring. In 18″ the stronger systolic contractions, having an amplitude of more than double the normal, appeared about every third

beat or more This lasted for 20″, and when the hyperpnœa was at its maximum, this great stimulation of the cardiac contraction began to pass off and to approach the normal in amplitude, reaching, a few seconds later, a still less amplitude of $\frac{2}{3}$ the normal and $\frac{1}{4}$ that of the stimulated condition. It was also irregular and a little slower (120 per min.) The administration of the anaesthetic lasted 60″, and 20″ later the irregularity had passed off but the beats were of the same rate with an amplitude still less, viz., about $\frac{1}{2}$ the normal. During the complete cessation of breathing the heart beats suffered no further, and were shown in equal number on both cardiogram and stethogram, and, indeed, they began to improve in amplitude before any sign of returning breathing. Complete recovery ultimately occurred.

This demonstrates an early stimulant action of ethyl chloride upon the heart, followed by some irregularity and weakening, but the organ remains active after the respiration has been paralysed.

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20 % ethyl chloride + 10 % CO_2 in air. (See Record A2, and notes, page 13.)

As the inhalation was begun, the beats were 140 per min. and strong. In less than 30″ the systole began to increase, becoming more so with hyperpnœa, the rapidity also increased. At the height of hyperpnœa the rate was 164 per min., and the amplitude of the systole was about double that at the beginning of inhalation. With the onset of paralysis of respiration the heart lost its exaggerated systole, and, as the paralysis continued, the heart's amplitude slightly diminished and it slowed a little. A few seconds of irregularity occurred, but regularity returned, and, with the resumption of breathing, increased and exaggerated systolic contractions were recorded.

This demonstrates that CO_2 increases the stimulation of the heart, which lasts longer, and the beat is better during respiratory paralysis than that with the same strength of E.C. in air.

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20 % ethyl chloride + 50 % oxygen in air. (See Records A3, 4, and 4a, and notes, pages 13 and 14.)

The latter half of the first experiment with this mixture was rendered useless (so far as the heart record is concerned) because of loosening of the pointer of the cardiograph.

At the beginning of inhalation the rate was 144 per min. The amplitude of the systolic contraction increased 50 % in 32″, when the respirations improved.

On fastening the pointer this mixture was readministered, when

The rate was 180 per min. After an inhalation of $2\frac{1}{4}'$ it was slower (120 per min.) with an amplitude increased about 50 %. Increased rapidity to 162 per min , with an amplitude about normal, followed. This was in turn succeeded by slowing and increased amplitude. With these alternations the heart tended towards slowing and strengthening. When the inhalation ceased in 6′ 10″ the rate was 93 per min. with a depth slightly above normal.

The early part of the first experiment shows a fair stimulation of the heart. In the second the amplitude was smaller, but it will be seen that when the breathing slowed (i.e., when the amount of oxygen inhaled was smaller) the heart became more rapid, whereas quicker breathing tended to slow the heart and increase its amplitude. The heart showed no sign of failure even after an administration of over 6′ in the second experiment.

Vagi Cut.

The vagi were cut before the following experiments were conducted.

20% ethyl chloride in air, vagi cut. (See Record A5, and notes, page 14.)

The heart, having lost the inhibitory action of the vagi, beat 220 per min. On the administration of 20% E.C. in air the heart gradually slowed down, and 1′ after the bag was attached, the beats were 160 per min., and the depth diminished to one half. When inhalation was stopped in 2′ 3″ the beats were 142 per min., and the amplitude still further reduced.

This demonstrates the weakening of the heart, and as the vagi have been cut it cannot be a central, but a local effect.

20% ethyl chloride + 10% CO_2 in air, vagi cut. (See Record A6 and notes, page 15.)

Immediately preceding the inhalation the heart beat was 204 per min., and the first effect was slight increase in amplitude and slowing—to 192 per min.—and after 1½′ its rate had fallen to 162 per min., and the amplitude to one half of what it was prior to administration of the mixture. 2½′ later, and until after the anaesthetic was withdrawn (after inhalation for 4½′), the beat had not fallen in rate, but the amplitude was still further lessened 50%. Artificial respiration was necessary for recovery.

Here again we see the gradual weakening of the cardiac muscle. The slight initial stimulation possibly results directly from the CO_2 in the mixture.

20% ethyl chloride + 50% oxygen in air, vagi cut. (See Record A7 and notes, page 15.)

As the administration was started the beat was 204 per min., which gradually diminished till in 2′ it was 186 per min. with slightly diminished force. After an inhalation of 4′ the heart was much slower and weaker, and rather irregular, being 168 per min. with an amplitude of ⅓ the normal.

Here again we find the beneficent effect of oxygen. Although weakening of the heart occurred the effect upon it after inhalation for 5′ was not so great as with the other mixtures.

The conclusions to be arrived at are that the heart is initially stimulated, but this rapidly passes off when hyperpnœa occurs, and that the rapid absorption of the vapour causes weakening and irregularity of the heart. With elimination of the anaesthetic regularity returns, and a good beat continues even during respiratory paralysis. That this is due not to a central action, but to an effect upon the heart

muscle itself, is learnt by comparing this with the experiment with the vagi cut. The heart weakens as with intact vagi, and retains a good beat even when respiration is paralysed. That no irregularity occurs is no doubt due to the fact that, there being no hyperpnœa, the E.C. was not absorbed with the same rapidity and effect as in the earlier experiment with vagi uncut.

The addition of CO_2 to the E.C. apparently acts as a cardiac stimulant because the increased systolic contractions persisted *throughout* the hyperpnœa, and are seen to have recurred when respiratory paralysis passed off. This would seem to be chiefly a central effect not being produced except slightly with cut vagi.

Oxygen added to E.C. vapour has a decidedly beneficial effect upon the heart.

Whenever the respiration rate diminished (i.e., when the oxygen inhaled was lessened) a quickening of the heart rate followed, whereas, with the more rapid breathing and consequent larger intake of oxygen, the heart beat slower and more strongly.

The beneficial effect of oxygen is probably due chiefly, if not entirely, to the fact that respiration is slower and more shallow, limiting the amount of E.C. inhaled. It may also directly nourish the cardiac muscle, although Wood and Cerna[10] believe that it has no direct influence upon circulation.

Experiment L. 25 % ethyl chloride in air, vagi intact. (See Record L and notes, page 24.) Needle in the heart.

The fact that three administrations, 15 %, 20 %, and 20 % respectively, had been given previously must be remembered, as such strengths of vapour must have produced a decided impression upon the heart. We see that 25 % E.C. in air caused marked weakening, verging on paralysis, of the heart which only recovered with artificial respiration. The cardiac beats were much stronger before

30 % ethyl chloride in air

was given, and great weakening of heart did not appear till after a longer administration. These results were evidently central effects, for they did not occur when the same concentration of E.C. vapour was given with *cut vagi*.

As a respiratory tracing was not taken it is impossible to say to what extent cutting the vagi impaired pulmonary ventilation so diminishing the intake of the vapour.

Experiment F.—15 % ethyl chloride in air, vagi intact. (See Record F1 and notes, page 22.)

This experiment was performed by plethysmograph, method No. 2 described on page 9. It will be seen that with this mixture the systolic (upward) stroke was strengthened, the rate remaining unchanged. After withdrawal of the anaesthetic increased diastole had occurred, as seen in the fall of the lever, and the systolic stroke was diminished.

20 % ethyl chloride in air, vagi intact. (See Record F1 and notes, page 22.)

Improvement in systole did not occur, but the strength of the beat was not affected till later. Before removal of the anaesthetic diastole had increased, and the amplitude of the systole had diminished with slight quickening of the heart.

These effects show that there is an early stimulation of the heart with the first administration, and that the later effect of inhalation is to cause dilatation of the heart muscle.

The *vagi were cut* at this stage.

15 % ethyl chloride in air, vagi cut. (See Record F2 and notes, page 23)

The effect of this mixture was similar to that produced by it when the vagi were intact, viz., fall of the lever into an increased diastolic position and diminution in the systole of the heart.

As mentioned in the notes, a control experiment was performed. Inhalation of

A bag of air (see Record F2 and notes, page 23)

produced no lowering of the lever nor diminution of the systolic stroke

15 % ethyl chloride + 46·6 % oxygen in air, vagi cut, and

15 % ethyl chloride in oxygen. (See Record F2.)

These respectively caused an identical fall in the lever with diastole and a diminished systole, the heart returning to the normal after removal of each.

15 % ethyl chloride + 6·6 % CO_2 in air, vagi cut. (See Record F3 and notes, page 23.)

Again the diastolic fall of the lever occurred with diminished systole, and this record shows (the drum not having been stopped) the gradual return of the heart to normal after removal of the anaesthetic mixture.

Conclusions.

This experiment shows that ethyl chloride initially stimulates the heart, and then produces weakening and dilatation by a direct action upon the heart muscle, the result being the same when central influence is removed by section of the vagi. It also supports the conclusion that CO_2 mixed with ethyl chloride has a central rather than a local action. We also learn that the combination of oxygen does not prevent dilatation of the heart by ethyl chloride.

Experiment M.

6·6 % ethyl chloride in air, vagi intact. (See Records M1 and 2 and notes, page 24.)

This experiment was performed with double tambours, the third method described on page 10 to show the effect upon the auricles and ventricles respectively.

Examination of the records and notes show that the ventricles are at first more affected than the auricles, and with repeated and continued inhalation the auricles more rapidly fail, so that ultimately both are about equally affected.

Blood Pressure Tracings. Although the examination of the B.P. tracings cannot give as satisfactory information regarding the heart as those of other methods yet points to be made out are valuable, and in one B.P. tracing (Record O_2) a fact is demonstrated which is not contained in any other record, viz., that with the B.P. at its lowest and with the heart beat gone, artificial respiration can be successfully used in restoring the animal. In giving us knowledge of that fact alone it is a valuable record.

That the heart muscle is affected directly and not through the centre is proven by experiments in which, with cut vagi, the effect is the same as with the nerves intact. There is also ample proof that the vagi are not paralysed by E.C., electrical stimulation even when breathing has stopped for 65″ causing fall of B.P., as seen in Records B3 and E4.

General conclusions as to the effect of ethyl chloride (by inhalation) upon the heart.

The initial action is one of stimulation which rapidly passes off, especially with hyperpnœa. and the subsequent effect is one of cardiac weakening and dilatation.

The ventricle is affected before the auricle which suffers more than the ventricle at a later stage.

The cardiac muscle is directly affected—a conclusion which is in accordance with those of Embley[3] and Webster[4].

Respiration is paralysed some time before the heart, and restorative measures are remarkably successful even after cardiac arrest.

CO_2 stimulates the heart by its action upon the centres, and has little, if any, local action.

The effect of oxygen is probably secondary by diminishing the depth and frequency of respiration, and so lessening the amount of ethyl chloride inhaled. It does not prevent cardiac dilatation.

Ethyl chloride does not paralyse the vagi. In this my results agree with those of Embley[3] and Webster[4] and are opposed to those of Cole[5].

PERFUSION OF THE HEART

(a) Of the frog ;
(b) Of the mammal.

The methods adopted have been described on page 10.

(a) *Perfusion of the frog's heart by Fuhner's method.*

Experiment P. (See Record P.)

The solutions used were—

Solution A—Blood (defibrinated) 50 c.c., Ringer sol. q.s. to make 565 c.c.

Solution B—Blood (defibrinated) 50 c.c., ethyl chloride 5 c.c., Ringer sol. q.s. to make 570 c.c., i.e., ·87 % E.C.

E.C. 1 = Sol. B. 20 c.c.
Ringer sol. 80 c.c.
i.e., ·174 % E.C.

E.C. 2 = Sol. B. 40 c.c.
Ringer sol. 60 c.c.
i.e., ·348 % E.C.

E.C. 3 = Sol. B. 60 c c.
Ringer sol. 40 c.c.
i.e., ·522 % E.C.

The normal beat of the heart after perfusion with Ringer only is seen, on substituting sol. E.C. 1, to be stimulated, followed by a slight irregularity which soon passed off, and on reperfusion, when recovery had occurred, stimulation is seen to have followed. This gradually passed off, and on substituting E.C. 2 sol. no stimulant action was forthcoming. E.C. 3 was then used with no effect upon the record, but it was noticed that blood, which passed through the heart, was venous in character so it was washed out with sol. A. Unless perfused rapidly the venous condition of the blood remained. The inner canula was withdrawn and a solution of adrenalin, 1 in 10,000, was pipetted directly into the heart. The stimulant effect is seen recorded after leaving adrenalin solution in the canula for 3′, it was withdrawn and E.C. 3 pipetted into the canula, causing immediate paralysis of the heart. The solution was withdrawn and adrenalin solution instilled with recovery of the heart. E.C. 1 sol. was substituted for the adrenalin solution, and the heart showed a tendency to paralysis in diastole, but soon recovered. On giving E.C. 2 sol. the heart slowed down and there was a tendency to twin beats. Instillation of E.C. 3 sol. into the canula caused paralysis of the heart, which was immediately overcome with adrenalin.

About an hour later the same heart was treated with five strengths of E.C. in Ringer-Blood Mixture, increasing the strength progressively. These solutions were pipetted into the canula and not perfused, and occasionally a few drops of

the respective mixtures were allowed to trickle over the surface of the heart. It was observed that this procedure was followed by slowing of the heart when no effect was produced by the corresponding mixture in the heart cavity.

The five strengths used were as follows :—

5 % Solution B. in Ringer's Solution.
10 % ,, ,,
15 % ,, ,,
20 % ,, ,,
30 % ,, ,,

The 5 % shows some stimulation of the heart without alteration of the rate. 10 % showed no appreciable result, but 15 % solution caused slight weakening of the beat. Dropping of the solution on the surface of the heart at once caused slowing, with increased amplitude of the beat which soon passed off. 20 % shows very slight stimulation in the amplitude with slight slowing, and the effect of application to the surface is again seen. 30 % causes a marked effect on the beat which was both slowed and diminished in amplitude. This is shown twice, whilst external application of the solution is seen to have markedly slowed and increased the amplitude of the beat.

Experiment Q. (See Record Q.)

Perfusion of frog's heart.

The method of performing this experiment is described on page 10, and the figures in brackets, which occur in the following paragraph, denote the figures in the record.

In this experiment the perfusion fluids were Ringer's solution containing various strengths of E.C., and a silhouette record was taken with a very slowly moving drum. After perfusing with Ringer, a saturated solution of ethyl chloride in Ringer (2) was substituted, and subsequent to a short period of stimulation rapid paralysis occurred. The anaesthetic was withdrawn and the heart washed out with Ringer.

After recovery, the perfusing fluid was as follows:—1 part sat. solution of E.C. in Ringer + 99 parts Ringer's solution (3). The amplitude of the beat was diminished. Removal of the fluid at once allowed of increase in amplitude, and with re-application caused marked diminution and slight slowing followed by a partial recovery. A few minutes later (6) the heart was again perfused with the same solution, and a gradual fall in amplitude occurred followed by a gradual rise, and during perfusion for about 1 hour and 40 minutes the amplitude became a little greater whilst the beats were grouped in twos, threes, &c., with an intermediate pause. Towards the end of the perfusion it will be seen that single beats of greater amplitude occurred at irregular intervals.

About 20′ later (8) a stronger perfusing solution was used, viz., 5 parts sat. sol. of E.C. in Ringer diluted with 95 parts Ringer's solution. This was perfused for 2 hours. The first effect was one of stimulation, but in about 6′ the normal amplitude was reached and almost immediately grouping of the beats began, becoming more and more distinct. But before the end of the experiment the grouping took on a different character, viz., 3 beats having the same amplitude alternated with 3 of a little greater amplitude, giving the record a "turretted" appearance. This grouping into threes was quite regular for several minutes, and whilst it occurred the intermediate rest, seen in the earlier part of the tracing, was absent.

5′ after cessation of the previous perfusion (10) a fluid of double the strength of the foregoing (i.e., 10 parts sat. sol. of E.C. in Ringer + 90 parts Ringer's sol.) was used, and a perfusion lasting 2 hours 25 minutes was started. Here again there was a slight initial stimulation, but with this concentration the slow beats and "turretted" appearance were less regular than with the weaker solution, and towards the end it was very irregular.

Perfusion of the frog's heart demonstrates that E.C. has an early stimulating effect. That strong solutions have a paralysing action which can be prevented by using weaker strengths. In experiment P. the strongest of the solutions used caused paralysis, even after stimulation with adrenalin solution. The arrhythmia or grouping of the beats is demonstrated slightly in experiment P, but by prolonged perfusion with a very slowly moving drum, as was done in experiment Q, it is shown apparently to be a result of a long administration—much longer than by inhalation either experimental or clinical. That it is muscular and not nervous in its origin is proven by the fact that in an experiment (see Record R) in which 1 % Liq. Atropinæ was placed in the pericardial sac of a frog for 15′ before suspension of the heart and tested electrically later, showed an almost immediate "twin beat" action on applying a sat. solution of E.C. in Ringer to the surface of the heart.

This grouping of beats is also seen in one experiment in which a rabbit's heart was perfused (see Records J2 and 3.) As will be mentioned later, the cause of that condition of heart beat was probably chilling of the organ ; and in support of this opinion a glance at Record R will show that washing of the suspended heart with warm saline quickened the beat.

(b) *Perfusion of mammal's heart by Brodie's apparatus.*

(The apparatus is described on page 10.)

Experiment H. (See Record H.)

Cat's heart (excised) perfused through the coronary arteries with ethyl chloride blood—Defibrinated blood 50 c.c., ethyl chloride 5 c.c., and Ringer's solution to make 565 c.c. (·87 %.)

The normal rate = 90 per min. With the first introduction of the E.C. blood into the heart, the beat slowed very slightly with greater systolic contraction. In

5″ the beat rapidly increased in rate to 140 per min., the amplitude being a little greater than normal. In 1′ this stimulation was suddenly followed by weakening, the rate being reduced to 88 per min. and the amplitude to ½ the normal. The perfusion, with the anaesthetic solution, was stopped in 2¼′ and Ringer's solution substituted, but the heart never recovered.

The heart was first slowed, then suddenly weakened, fatal paralysis following.

Experiment I. (See Records I 1 and I 2.)

Rabbit's heart (excised) was perfused through the coronary arteries.

The following solutions were used :—

E.C. (a) = 1 c.c. ethyl chloride in 100 c.c. defibrinated blood + 300 c.c. Ringer-Locke solution, i.e,, 1 in 400 or ·25 %

E.C. (b) = 1 c.c. E.C. in 100 c.c. blood + 400 c.c. Ringer-Locke solution, i.e., 1 in 500 or ·20 %

E.C. (c) = 1·4 gram (1·52 c.c.) E.C. in 100 c.c. defibrinated blood + 400 c.c. Ringer-Locke solution, i.e., 1 in 328 or ·304 %

Ether Blood = ·7 c.c. ether in 100 c.c. defibrinated blood + 400 c.c. Ringer-Locke solution.

$CHCl_3$ Blood = ·8 c.c. $CHCl_3$ in 100 c.c. defibrinated blood + 400 c.c. Ringer-Locke solution.

The normal rate of the heart when perfused with Ringer was 78 per min. with E.C. (a) solution.

There was at once slight irregularity with slight increase in rate. In 10″ rapid failure occurred, there being marked decrease both in rate to 39 per min. and in amplitude to ⅕ of the normal. Perfusion with Ringer solution and Ringer and blood caused complete recovery, the rate being slower, 64 per min., and the amplitude greater with the blood solution. Ether-blood mixture was then introduced, and markedly stimulated the rate of the heart. In 100″ it was 75 per min., and the amplitude equal to that prior to the introduction of the ether, and on ceasing the ether perfusion, which had lasted 4′ 50″, the rate was 100 per min., and the amplitude almost as great as normal.

On perfusion with Blood-Ringer solution, the beat fell to 87 per min., with the same amplitude. Solution E.C. (b) was then introduced. After 1′ the amplitude began to fail, and 1′ later, when it was about ½ of the normal, the amplitude suddenly showed an irregularity, some of the beats being stronger than others. This remained unaltered during the further 3′ that the perfusion was carried on, but the rate increased to 100 per min. Having been weakened the heart was stimulated with ether-blood solution.

E.C. (3) was given when the rate was 60 per min. with good amplitude, and in 20″ the amplitude began to suffer, falling to less than ½, whilst the rate was not proportionately increased, being 75 per min. After perfusion for 4′ the anaesthetic

was withdrawn, and the amplitude gradually returned to normal with a rate of 54 per min. The effect of $CHCl_3$ blood solution was tested, and in 3′ the heart was almost paralysed, and a little later completely so.

This experiment goes to prove that ethyl chloride has a slight initial stimulant effect on the heart, and that the stronger the solution the more rapidly does depression result. That E.C. (b) solution, although only a little weaker than E.C. (a) was perfused for a very much longer period, and without the same profound depression is doubtless due to the fact that the heart had shortly before been greatly stimulated by ether. That previous stimulation of the heart, however, does not prevent depression by ethyl chloride, if sufficiently concentrated, is shown by the fact that E.C. (c) (the strongest of the three solutions) quickly caused depression although the heart had been stimulated by ether between the withdrawal of E.C. (b) and the introduction of E.C. (c). An important point with regard to this latter solution is that although it caused a great depression within a few seconds a fairly long perfusion did not alter much further the amplitude of the beat.

Experiment J. (See Records J1, 2 and 3.)

Rabbit's heart (excised) was perfused through the coronaries.

The following was the solution used :—

50 c.c. of ·5 % ethyl chloride solution in defibrinated blood.

400 c.c. Ringer's solution, i.e., a Blood-Ringer solution of ethyl chloride having a strength of ·06 %.

The rate of beat whilst perfusing with Ringer was 104 per min., and when the ·06 % solution of E.C. was introduced into the heart the rate was 84 with almost double the amplitude, and after perfusion for 2′ the rate was 78, and the amplitude increased about 27 %. Oxygenated defibrinated blood solution was substituted, and the rate slowed greatly—to 30 per min.—whilst the amplitude was not much increased, but the beats varied, some being exaggerated.

The E.C. Blood solution ·06 % was again perfused, and the heart slowed slightly (27 per min.), the amplitude not altering. After perfusing for 6′ the beats were very slow, there being intervals of 25″ and 30″ between the beats. Oxygenated blood was again used, and after 1′, during which there were only 3 beats, the rate increased, but on alternating the two profusion fluids several times this slow irregular beat remained, and towards the end "twin beats," similar to that were obtained with the suspended heart of the frog, appeared. This tremendous slowing of the heart was undoubtedly due to some other cause than ethyl chloride, probably chilling of the heart. The records, therefore, are useless for my purpose, except perhaps the beginning of J1 which shows an initial stimulating action of E.C.

Experiment K. (See Records K1 and K2.)

Cat's heart (excised) was perfused through the coronaries.

The following was the ethyl chloride solution used :—

80 milligrammes ethyl chloride in 100 c.c. of a mixture of Ringer-Locke solution and blood, *i.e.*, a ·08 % solution of ethyl chloride.

Perfusion of the heart with Ringer-Locke blood showed a rate of 24 per min. just before E.C. The beat with the anaesthetic solution very soon began to lose its force, and in about a minute the amplitude was diminished by almost a half, the rate being 20 per min. 3′ later a series of large and small beats was recorded, the stronger ones becoming less and less frequent, and the beats becoming slower (12 per min.), until the perfusion was stopped 6½′ after the irregularity appeared. About 5′ later perfusion with the E.C. solution was recommenced with a rate of 18 per min., 4′ later the rate was unaltered, but the amplitude was diminished. With further perfusion the rate increased to 26, and still later to 32 per min., the amplitude having diminished to a very great extent.

This experiment also demonstrates the gradual failure of the heart by perfusion with E.C. in Ringer-Locke-blood solution.

Conclusions from the perfusion of the heart of the frog and of the mammal are that E.C. slightly stimulates the heart at first and that this is soon followed by depression, the appearance of which is earlier with the stronger solutions. Stimulation with ether greatly extends the time during which ethyl chloride can be administered, although it does not prevent cardiac depression.

III. THE EFFECT OF ETHYL CHLORIDE ON THE BLOOD VESSELS.

(a) By perfusion of the suspended frog ;
(b) By volume records of the kidney.

(a) *Perfusion of the blood vessels of the suspended frog.*

The method employed for this is described on page 11.

The solution of E.C. used in first experiment was—50 c.c. defibrinated blood, 515 c.c. Ringer's solution, 5 c.c. ethyl chloride.

Experiment R.

Perfusion with—

Drops per min.

1 Ringer's Sol.	2 E.C. Sol.	3 E.C. Sol.	4 Ringer's Sol.	5 E.C. Sol.	6 Adrenalin
17	11	10	11	13	8
9	10	10	8	12	6
7	8	10	9	10	6
5	7	9	9	10	5
5	6	9	10	10	4
	5	10	11	8	4
			14		3
			16		3
			18		
			22		
			27		
			29		
			29		

Experiment S.

In this experiment the E.C. solution used was equal parts of that used in experiment R and Ringer.

Perfusion with—

Drops per min.

1 Ringer	2 E.C. Blood Sol. ½ strength	3 Ringer	4 E.C. Blood Sol. ½ strength	5 Ringer	6 E.C. Blood Sol. ½ strength	7 Ringer	8 Adrenalin
66	42	34	33	47	53	34	16
60	33	40	30	58	43	37	12
57	27	46	27	69	37	36	10
55	24	52	27		34	42	10
55	18	58	26		31	42	9
		63	25			48	8
			24			46	7
							7
							7

During this experiment not only were the drops which fell in a given time counted but also the time taken for a given amount to fall. The following was the result:—Between the 6th and 7th of the above series, 5 c.c. of the E.C. blood sol. dropped in 5½′ and 10 c.c. in 11′. After the 7th series, 10 c.c. of Ringer's sol. dropped in 5′, and a further 10 c.c. fell in 4½′, i.e., 10 c.c. of E.C. blood sol. took more than twice as long to fall as that amount of Ringer's sol.

Further, the number of drops of the respective liquids required to make 1 c.c. was counted, and it was found that 28 drops of the E.C. blood mixture = 1 c.c., and 23 drops of Ringer = 1 c.c.

A simple calculation shows that

25·45 drops of E.C. blood sol. and 46 drops of Ringer

was the average number that fell per min.

Had series 6 been prolonged a further diminution would have occurred.

These experiments admit of the conclusion that ethyl chloride causes contraction of the blood vessels of the frog.

(b) *Volume Records of the Kidney.*

Experiment C.

See Records C1 to C7 and notes, page 17.

Seven administrations were conducted, viz., 4 with vagi intact and 3 with vagi cut, and in every one was there a steady fall in the K.V. To indicate the fall, the height in c.m. of the tracing from the base line was measured, and the following table shows at a glance the extent of the fall in each case.

	Initial height above base line.		Late height above base line.
Vagi intact.			
10% E.C. ...	fall from 11·1 c.m.	...	to 10·4 c.m.
20% E.C. ...	,, 11 c.m.	...	,, 10 c.m.
20% E.C. ...	,, 11·3 c.m.	...	,, 10·3 c.m.
25% E.C. ...	,, 11·4 c.m.	...	,, 9·5 c.m.
Vagi cut.			
10% E.C. ...	,, 10·9 c.m.	...	,, 8·7 c.m.
20% E.C. ...	,, 11·7 c.m.	...	,, 9·7 c.m.
25% E.C. ...	,, 11·1 c.m.	...	,, 9·4 c.m.

The general fall in K.V. demonstrated by these figures conclusively proves that the blood content of the kidney is diminished, therefore that contraction of the vessels results.

Only in the very late stage when the B.P. is almost at its lowest do the vessels show evidence of dilatation.

Records C5 and C7 show that when the B.P. was greatly diminished just before withdrawal of the anaesthetic the K.V. began to rise—a paralytic dilatation—the latter record fortunately shows more than the former because the drum was moving during the recovery, and a study of it shows that during

the early stage of the artificial respiration the K.V. was still increased, but before it was stopped the volume began to fall, and continued to do so for a short time longer on account of the vessels regaining their tone. The increase in volume which followed was the normal recovery of the K.V. as the effect of the E.C. passed off.

Vascular paralysis, although very late, appeared before cardiac paralysis, the heart beats showing well in the B.P. tracing during the whole period of dilatation of the vessels.

Conclusions.

The general conclusions as to the effect of E.C. upon the blood vessels from experiments upon the frog and mammal are undoubtedly that it causes contraction, except in the very late stages with greatly lowered B.P. when paralysis of the vessels occurs. Restorative measures quickly improve the tone of the vessels. Paralysis of the vessels occurs before that of the heart.

My results agree with that of Cole[5] who found that "intestinal volume increased with a rise in blood pressure, and decreased with a fall." Embley's[3] experiments led him to the conclusion that relaxation is produced ; mine, that this does not appear until a very late stage ; whilst Webster[4] found that the volume of organs follows passively the change in blood pressure.

SUMMARY.

The experimental data in the foregoing pages seem to me to place upon a more scientific basis what has, to some extent, been quite empirical in the clinical use of ethyl chloride as a general anaesthetic. Although known to possess anaesthetic properties more than half a century ago it failed in being generally adapted because of the want of knowledge of certain facts, and even so recently as 1901, when I first saw it used, it proved disappointing, not from the difficulty of storing it, but from the fact that its method of administration was wrong. As administered at that time there was no rebreathing permitted, yet I think it has been shown that small proportions of CO_2 are of great utility. From my clinical experience of the drug (which has been fairly considerable) I can hardly conceive a more satisfactory method of administration than that adopted now of allowing the patient to breathe and rebreathe the vapour from a bag. The results are excellent so long as the inhaler is not applied long enough to produce cyanosis. Carbonic acid, being a cardiac stimulant, tends in small proportions to prevent a rapid weakness of the heart muscle, and it is also a respiratory stimulant.

Another clinical fact (of this, I am glad to say, my experience has been very limited) is the ready response to restorative measures in cases of difficulty. Personally, I have only once been present when death has occurred whilst ethyl chloride was being administered, and in that case the patient had already been given a little chloroform prior to the administration of the ethyl chloride. I have seen a few cases of arrest of breathing and collapse, but in every instance vitality was restored by artificial respiration. It having been shown that respiration may fail with the chest in a deep expiratory position, I should have no hesitation in case of need to attempt forcible inflation of the lungs by blowing strongly into the patient's mouth to fill the chest. This method proved very efficient during this investigation where respiratory paralysis occurred from inhaling vapours of different degrees of concentration.

Clinically anaesthetists are familiar with the fact that respiration fails before the heart, and my investigations upon animals amply prove this fact to be true, and when CO_2 is inhaled with ethyl chloride the heart beats more actively during respiratory paralysis than when arrangements are made whereby no CO_2 will be inhaled.

My experiments with oxygen show how it increases the safety of ethyl chloride, and clinically I believe that the class of case in which this combination would be of advantage is where already respiratory embarrassment exists, and in which a weak vapour in air would prove of little, if any, use as an anaesthetic. By giving a strong vapour in oxygen a satisfactory anaesthesia could be produced.

Another fact must here be referred to. Anaesthetists know that it is a very general rule that if a patient becomes quickly anaesthetised he soon recovers, whereas slowly produced anaesthesia gives a longer period of unconsciousness.

The explanation of this may be gathered from the extracts I have made from the papers of Camus and Nicloux, which show that with slower absorption a much larger amount of ethyl chloride is taken up by the blood without causing death of the animal. Clinically, hyperpnœa quickly causes anaesthesia, and unless the administration is stopped early, respiration suffers. Better anaesthesia is obtained when the absorption has not been rapid. I have had experience, clinically, of a few cases in which anaesthesia was very slowly, and with difficulty, induced, and then only with large doses of the drug, in which consciousness returned very quickly. Just as is seen at times with other anaesthetics—nitrous oxide, ether, and chloroform—such patients frequently are alcoholics, but this may occur in the most abstemious, and no explanation can at present be given except by resort to the "personal element" theory.

The following paragraphs give the salient features regarding this thesis :—

Blood Pressure. Ethyl chloride produces initially a slight rise and then, except with weak vapours, a fall in B.P. This is undoubtedly cardiac in origin. The higher the percentage of vapour inhaled the greater and more rapid is the fall. Administration of oxygen with ethyl chloride diminishes very greatly the depth and rate of fall of B.P. Large proportions of CO_2 increase the rapidity of fall.

Respiration is first stimulated, in some instances very markedly, then with strong vapours it is depressed, and later paralysed. The stimulation is chiefly the result of stimulation of the afferent fibres of the vagus and to a less extent of the respiratory centre. Respiration is paralysed before the heart, and the greater the hyperpnœa in the early stage the more rapidly does paralysis ensue. Paralysis sometimes occurs with the chest in a deep expiratory position.

Heart. There is first stimulation and then weakening with dilatation of the cardiac muscle, the effect being directly as the strength of ethyl chloride used. The action is directly upon the heart and not through the centres. Stimulation of the heart does not prevent, although it will delay, depression by ethyl chloride of sufficient concentration given subsequently. The heart beat persists for some time after respiration has been paralysed.

The Vagus is not paralysed. Stimulation of the afferent fibres is an important element in respiratory stimulation. Electrical stimulation of the nerve even during respiratory paralysis caused immediate fall of blood pressure.

The Blood Vessels are contracted by ethyl chloride except in the very late stages. Artificial respiration quickly restores their tone.

The Blood takes up varying amounts of ethyl chloride. The slower it is inhaled the greater will be the amount absorbed by the blood. The corpuscles retain about three times as much as the plasma, and by combining loosely with the drug the blood probably acts as a restraining agent, converting an irregular into a constant flow.

The Danger associated with the administration of ethyl chloride is not in the amount inhaled but in the *concentration* of the vapour presented for inhalation.

Oxygen administered with ethyl chloride greatly increases its safety from the fact that the rate and depth of breathing are diminished with consequent lessening of the intake of anaesthetic vapour. Artificial respiration was not required in any of the experiments in which oxygen was used, although in some, high percentages of ethyl chloride vapour were given. The addition of oxygen does not prevent cardiac dilatation.

Carbonic Acid stimulates the heart and respiration, and in small amounts is beneficial, but large proportions mixed with ethyl chloride vapour more rapidly paralyse respiration and lower blood pressure. Its action upon the heart is central, but in stimulating respiration its effect is almost entirely local by stimulating the afferent fibres of the vagi.

Artificial Respiration is very effective in restoring respiration, and even when the heart is paralysed recovery can result. Forcible inflation of the lungs proved eminently satisfactory when required during the experiments.

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